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).

# CLINICAL STUDY PROTOCOL

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

Short Title: A Phase 1 Study of TAK-385 in Hormone Treatment-naive Patients With Prostate Cancer

**Sponsor:** Takeda Pharmaceutical Company Limited
1-1 Doshomachi 4-chome, Chuo-ku, Osaka

**Study Number:** TB-AK160108

**Version** Amendment 2

**IND Number:** NA **EudraCT Number:** NA

**Study Drug:** TAK-385

**Date:** 1 July 2015

## Amendment History:

| Date | Amendment Number | Region |
|---|---|---|
| 12 February 2014 | Initial Protocol | All sites |
| 23 January 2015 | 1 | All sites |
| 1 July 2015 | 2 | All sites |

# 1.0 STUDY ADMINISTRATION INFORMATION

## 1.1 Contacts and Responsibilities for Study-Related Activities

A separate contact information list will be provided to each site.

## 1.2 Principles of Clinical Studies

This study will be conducted with the highest respect for the individual participants in accordance with requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

## 1.3 Protocol Amendment Summary of Changes

This document describes the changes in reference to the Protocol Incorporating Amendment No. 2.

The primary purpose of this amendment is to update the protocol regarding the addition of a new cohort, Cohort 4, to Part A. Minor grammatical and editorial changes are also included. Detailed description of amendments to texts are given in Appendix J. The following is a summary of the changes made in the amendment:

1. Addition of a new cohort, Cohort 4 (loading dose of 360 mg and a maintenance dose of 120 mg) to Part A.
   Justification: 320 mg or 360 mg may be selected as the loading dose in the planned phase 3 multinational study. Based on this situation, a new cohort, Cohort 4, is added to Part A, designed to evaluate the tolerability of loading dose of 360 mg in Japanese patients before joining the phase 3 multinational study.
2. Correction of inconsistencies within the original protocol.

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## LIST OF APPENDICES

## 2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor:<br>Takeda Pharmaceutical Company Limited</td><td colspan="2">Study Drug:<br>TAK-385</td></tr>
<tr><td>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</td><td>IND Number:<br>NA</td><td>EudraCT Number:<br>NA</td></tr>
<tr><td>Study Number: TB-AK160108</td><td colspan="2">Phase: 1</td></tr>
<tr><td colspan="3">Study Design:<br>This study consists of two parts: Part A, a dose-rising phase, and Part B, an expansion phase.<br>In Part A, three to six patients will be enrolled in each cohort. Whether or not the study will proceed to the next cohort or Part B will be determined through assessment of tolerability at the dose in question, based on the incidence of dose-limiting toxicity (DLT) in the evaluation period. TAK-385 will be taken once a day for 28 days at the doses assigned to each cohort. Cohort 1 will receive a loading dose of 320 mg and a maintenance dose of 80 mg, Cohort 2 will receive a loading dose of 320 mg and a maintenance dose of 120 mg, Cohort 3 will receive a loading dose of 320 mg and a maintenance dose of 160 mg, and Cohort 4 will receive a loading dose of 360 mg and a maintenance dose of 120 mg. Patients being switched to a gonadotropin-releasing hormone (GnRH) agonist (eg, leuprorelin) or a GnRH antagonist (eg, degarelix) following the completion of TAK-385 treatment in Part A will first pass through a 1-week observation period (except for study withdrawals). Whether or not the study will proceed to Part B will be determined by the study sponsor after consulting the study monitoring committee (SMC) based on a comprehensive evaluation of the tolerability and safety data from Cohort 2 of Part A.<br>In Part B, subjects will be randomized to receive study drug (TAK-385 loading dose of 320 mg and maintenance dose of either 80 mg or 120 mg – equal numbers of subjects will be randomized to 80 mg and 120 mg) once a day orally to evaluate safety. In addition to the safety assessments, efficacy assessments will also be performed according to the study schedule, and study drug will be administered until the discontinuation criteria (Section 7.5) are met for each individual subject. After completing 48 weeks of treatment, subject may, at the discretion of the investigator, and depending on the wishes of the subject, continue receiving study drug (for a maximum of 96 weeks), or they may complete the study and be switched to a GnRH agonist or a GnHR antagonist, starting from the day after the day of the last dose of TAK-385.<br>All subjects who receive study drug will undergo safety follow-up 30 to 40 days after the last dose of TAK-385.</td></tr>
<tr><td colspan="3">Part A (Dose-rising phase)<br>Primary Objectives:<br>To evaluate the tolerability and safety of TAK-385 in hormone treatment-naive patients with non-metastatic prostate cancer.<br>Secondary Objectives:<br>To evaluate the pharmacokinetics (PK) and the effects on serum testosterone of TAK-385 in hormone treatment-naive patients with non-metastatic prostate cancer.<br>Part B (Expansion phase)<br>Primary Objectives:<br>To evaluate the safety of TAK-385 in hormone treatment-naive patients with non-metastatic prostate cancer.<br>Secondary Objectives:<br>To evaluate the change over time in the prostate-specific antigen (PSA) levels and the PK and effects on serum testosterone of TAK-385 in hormone treatment-naive patients with non-metastatic prostate cancer.</td></tr>
</table>

<table>
<tr><td colspan="2">Subject Population: Japanese patients with hormone treatment-naive non-metastatic prostate cancer</td></tr>
<tr><td>Numbers of Subjects<br>Part A: 3 to 6 subjects in each cohort (3 to 24 subjects in total)<br>Part B: 15 subjects in each group (30 subjects in total)</td><td>Number of Sites<br>Part A: 2 to 3 sites<br>Part B: Approximately 7 sites (some of the sites will be the same as the sites in Part A)</td></tr>
<tr><td>Dosage<br>Dosage: TAK-385 once a day orally at least 30 minutes before breakfast<br><u>Part A</u><br>Cohort 1: Loading dose of 320 mg and maintenance dose of 80 mg<br>Cohort 2: Loading dose of 320 mg and maintenance dose of 120 mg<br>Cohort 3: Loading dose of 320 mg and maintenance dose of 160 mg<br>Cohort 4: Loading dose of 360 mg and maintenance dose of 120 mg<br>(Additional cohort: Loading dose of 320 mg and maintenance dose of 40 mg)<br><u>Part B</u><br>80 mg group: Loading dose of 320 mg and maintenance dose of 80 mg<br>120 mg group: Loading dose of 320 mg and maintenance dose of 120 mg<br>(If there is an additional cohort in Part A, then instead of a 120 mg group, there will be a 40 mg group, which will received a loading dose of 320 mg and a maintenance dose of 40 mg.)</td><td>Route of Administration<br>Oral</td></tr>
<tr><td>Duration of Treatment<br>Part A: 28 days<br>Part B: 48 weeks (may be continued for up to a total of 96 weeks maximum)</td><td>Period of Evaluation<br>Part A: Approximately 2 months<br>Part B: Approximately 1 year (approx. 2 years if therapy is continued)</td></tr>
<tr><td colspan="2">Main Criteria for Inclusion<br>1. Patients with histologically or cytologically confirmed prostate cancer<br>2. Patients whose clinical diagnosis is T1-4 N0 M0, or Tx N0 M0 for patients who have undergone radical prostatectomy<br>3. Patients who have not received hormone therapy (eg, GnRH agonist, GnRH antagonist, steroidal antiandrogen, non-steroidal androgen) for prostate cancer<br>4. Patients with serum testosterone at screening > 150 ng/dL<br>5. Patients meeting either of the following criteria for PSA at screening<br>Untreated prostate cancer: PSA at screening > 4.0 ng/mL<br>Treated prostate cancer: PSA at screening > 0.2 ng/mL<br>6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1</td></tr>
</table>

**Main Criteria for Exclusion**

1. Patients exhibiting symptoms judged related to prostate cancer by the investigator (eg, bone pain, pelvic pain, ureteral obstruction) who urgently require hormone therapy such as GnRH agonist, GnRH antagonist, or combined androgen blockade (CAB)/maximum androgen blockade (MAB) therapy, chemotherapy, or radiotherapy
2. Patients who have received 5-alpha reductase inhibitors (except for patients who have been treated for male-pattern alopecias)
3. Treatment with any investigational compound within the 4 weeks (28 days) prior to the first dose of study drug or ongoing participation in another experimental trial related to the treatment of prostate cancer
4. Known hypersensitivity to TAK-385, TAK-385 excipients, or GnRH antagonists
5. Clinically relevant ECG abnormalities, or the following ECG abnormalities, at screening
   - Q-wave infarction, unless identified 6 or more months prior to TAK-385 treatment initiation
   - Fridericia corrected QT (QTcF) interval > 450 msec (when calculating the QTc interval, Fridericia's equation [$QT/RR^{0.33}$] will be used)
6. Patients with congenital QT prolongation

**Endpoints**

Part A

Primary endpoints

- DLTs, adverse events (AEs), clinical laboratory tests, vital signs, and 12-lead ECGs

Secondary endpoints

- Plasma concentrations of unchanged TAK-385
- Serum testosterone concentrations

Part B

Primary endpoints

- AEs, clinical laboratory tests, vital signs, and 12-lead ECGs

Secondary endpoints

- PSA levels
- Plasma concentrations of unchanged TAK-385
- Serum testosterone concentrations

**Statistical Consideations**

Safety analyses

1) Incidences of AEs

The following analysis will be performed for the safety analysis set.

Treatment-emergent adverse events (TEAEs) will be tabulated by part and dose. TEAEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT).

2) DLTs

The following analysis will be performed for the DLT analysis set.

The incidences of TEAEs judged to be DLTs in Part A will be tabulated by PT and dose.

3) Clinical laboratory test value profiles, vital signs, and 12-lead ECGs

The following analyses will be performed for the safety analysis set.

For continuous data, summary statistics will be calculated for the baseline values, the values observed at each assessment time point, and the changes from baseline by part and dose.

For categorical data and assessments based on reference values, cross tabulation of the values before and

after treatment (eg, normal/abnormal, qualitative clinical laboratory test values) will be performed by part and dose for each test parameter.

Pharmacokinetic analyses

Pharmacokinetic parameters (eg, maximum observed plasma concentration [Cmax], area under the plasma concentration - time curve [AUC]) will be evaluated using the plasma TAK-385 concentrations, and summary statistics will be calculated for the plasma concentrations and each of the pharmacokinetic parameters. Figures showing the changes over time in the plasma concentration of TAK-385 will also be prepared.

**Rationale for the Planned Sample Size**

Part A

Each cohort will have 3 or 6 subjects, based on the the guidelines on the clinical evaluation of antineoplastics

Part B

In order to detect less frequent AEs, 15 subjects per group (total of 30 subjects) were established as the number of cases enabling an approximately 80% chance of detecting AEs characterized by a true incidence of 10%.

## 3.0 LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| AMS | Aging Male's Symptoms |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the plasma concentration-time curve |
| BMI | body mass index |
| BMP | di-docosahexaenoyl (22:6)-bis(monoacylglycerol) phosphate |
| CAB | combined androgen blockade |
| CK-MB | creatine kinase MB |
| Cmax | maximum observed plasma concentration |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DHT | dihydrotestosterone |
| DLT | dose-limiting toxicity |
| eCRF | electronic case report form |
| ECOG | Eastern Cooperative Oncology Group |
| EORTC | European Organization for Research and Treatment of Cancer |
| EPIC | Expanded Prostate Cancer Index Composite |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GnRH | gonadotropin-releasing hormone |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| ICH | International Conference on Harmonisation |
| IEC | independent ethics committee |
| IRB | institutional review board |
| LFT | liver function test |
| LH | luteinizing hormone |
| MAB | maximum androgen blockade |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NOAEL | no-observed-adverse-effect level |
| PK | pharmacokinetics |
| P-gp | P-glycoprotein |
| PGx | pharmacogenomics |
| PSA | prostate-specific antigen |
| PT-INR | Prothrombin Time-International Normalized Ratio |

| | |
|---|---|
| PTE | Pretreatment Event |
| QTc | corrected QT (interval) |
| QTcB | Bazett corrected QT |
| QTcF | Fridericia corrected QT |
| SHBG | sex hormone binding globulin |
| SMC | study monitoring committee |
| Tmax | maximum drug concentration time |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |

# 4.0 INTRODUCTION

## 4.1 Summary

In 2008 prostate cancer reached approximately 900,000 cases/year worldwide and is now the second leading cancer in men, accounting for 13.7% of cancer cases in men [1]. The median age of diagnosis is 70, and prostate cancer is rarely diagnosed in men under 40 [2]. Incidence increases with age and is expected to rise in the future as the population ages. In Japan, 2008 statistics show that prostate cancer ranks a high fourth in morbidity among cancers in men [3]. Prostate cancer in Japan also occurs more often with age, and the incidences increases rapidly in men 60 and older.

It is known that prostate cancer is to responsive to surgical castration and that the effectiveness of this therapy results from the elimination of androgen. This knowledge led to the understanding that most prostate cancers are growth hormone dependent and ever since this discovery, hormone therapy has played an important role in the treatment of prostate cancer.

Castration by orchiectomy or a gonadotropin-releasing hormone (GnRH) agonist is the main mode of therapy for localized progressive and metastatic cancers, and GnRH agonists such as leuprorelin acetate are widely used [4]. When multiple doses of a GnRH agonist are administered, a temporary increase in gonadotropin secretion (flare up) occurs. That is followed by a decrease in responsiveness (desensitization) in the pituitary gland and gonads, which appears to work effectively by inhibiting the secretion of sex hormones. The flare up sometimes leads to a temporary worsening of symptoms, and the effectiveness of GnRH agonist begins to appear about 3 to 4 weeks after the initial dose. In addition, the GnRH is a peptide formulation and is unable to be administered orally. Consequently, development of a new medication that is easy to administer and does not cause flare ups is needed.

TAK-385 is a non-peptide orally active GnRH antagonist with a novel structure that was discovered by Takeda Pharmaceutical Company, Ltd. TAK-385 antagonizes GnRH at the GnRH receptors present in the basophils (secreting cells) of the anterior pituitary gland and inhibits the GnRH-stimulated secretion of gonadotropin luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from those cells. This action lowers the serum testosterone concentration in the blood. An antitumor effect is expected in prostate cancer patients due to the suppression of serum testosterone production by the testes. TAK-385 is also expected to manifest its effects rapidly without causing flare ups like GnRH agonists. Moreover, because it is a non-peptide formulation, TAK-385 can be administered orally, unlike peptide-based GnRH agonists that must be absorbed subcutaneously. The clinical pharmacokinetic and pharmacodynamic profiles may offer additional advantages compared with a depot peptide formulations, such as more rapid recovery from short term medical castration.

Takeda Pharmaceutical Co., Ltd. decided to develop TAK-385 for the treatment of prostate cancer both overseas and in Japan. Moreover, development of TAK-385 in Japan and Asia for endometriosis and uterine fibroids is already underway.

### 4.1.1 Nonclinical Summary

#### 4.1.1.1 Pharmacology Related to the Proposed Mechanism of Action

A series of in vitro and in vivo pharmacological studies have demonstrated that TAK-385 acts as a potent and highly selective antagonist for human GnRHR (hGnRHR).

[redacted] [5].

#### 4.1.1.2 Safety Pharmacology

In safety pharmacology studies, [redacted] [5].

#### 4.1.1.3 Pharmacokinetics and Product Metabolism in Animals

[redacted]

[5].

#### 4.1.1.4 Toxicology

TAK-385 has been evaluated for safety in single- and repeat-dose toxicity studies, with supportive toxicokinetic analyses, in mice, rats, and monkeys. Genetic, carcinogenicity, reproductive, and phototoxicity studies have also been performed.

[redacted]

[5].

[redacted]

### 4.1.2 Clinical Studies

4.1.2.1 Japanese Phase 1 Single- and Multiple-dose Study ([redacted])

A placebo-controlled double-blind single dose study of the safety, pharmacokinetics (PK), and pharmacodynamics of TAK-385 was conducted in 72 premenopausal healthy adult Japanese women (including 12 in the placebo group). Moreover, a crossover study comparing fasted state/postprandial administration, and fasted/preprandial administration was conducted in 24 premenopausal healthy women to investigate the effect of meals on TAK-385 PK. In addition, a placebo-controlled double-blind, 14-day multiple dose study of safety, PK, and pharmacodynamics during of TAK-385 was conducted in 48 premenopausal healthy adult women (including 12 in the placebo group).

[redacted]

[redacted]

[5].

4.1.2.2 Overseas Phase 1 Single- and Multiple-dose Study ( )

A placebo-controlled double-blind single-dose study of the safety, PK, and pharmacodynamics of TAK-385 was conducted in 72 premenopausal healthy adult American women (including 12 in the placebo group). Moreover, a crossover study comparing fasted with fed (post-breakfast) administration was conducted in 12 premenopausal healthy women to investigate the effect of food on the PK of TAK-385. In addition, a placebo-controlled double-blind, 14-day multiple dose study of safety, PK, and pharmacodynamics during of TAK-385 was conducted in 36 premenopausal healthy adult women (including 9 in the placebo group).

[5].

4.1.2.3 Japanese Phase 1 Study of Drug-drug Interactions With Erythromycin ( )

A phase 1 open-label drug-drug interaction study was carried out in healthy Japanese male and female subjects to evaluate the effect of multiple doses (300 mg, q.i.d.) of erythromycin (moderate CYP3A4 inhibitor and P-gp inhibitor) on the single-dose PK of TAK-385 (20 mg).

[5].

4.1.2.4 Overseas Phase 1 Drug-drug Interaction Study ( )

[redacted] [5].

4.1.2.5 Overseas Phase 1 Single- and Multiple-dose Study (TAK-385_C27001)

Study C27001 was a phase 1 study that evaluated the safety, tolerability, PK, and PD of TAK-385 in 176 healthy English adult male subjects (128 subjects received TAK-385) receiving single doses of TAK-385 up to 360 mg QD and multiple doses of TAK-385 up to 180 mg QD for up to 28 days. The study had 4 parts: Part 1 included single-dose administration of TAK-385 to 32 subjects across 4 dose cohorts plus placebo and had a fed/fasted arm; Part 2 included multiple dose administration of TAK-385 for 14 days to 40 subjects across 5 dose cohorts plus placebo; and Parts 3 and 4 included multiple dose administration of TAK-385 for 28 days to 66 and 38 subjects, respectively, across 2 dose cohorts (a total of 4 dose levels), plus placebo.

There were no deaths or SAEs following single-dose or multiple-dose treatment with TAK-385 for 14 or 28 days.

Following 28 days of QD dosing, there were 3 discontinuations due to drug-related, hepatic AEs: 2 subjects in the 160 mg dose cohort in Part 3 of the study discontinued treatment due to Grade 1 AEs of hepatic enzyme increased (ALT and AST); and 1 subject in the 60 mg dose cohort in Part 4 of the study discontinued treatment due to a Grade 2 AE of liver function test (LFT) abnormal (ALT and AST). There was no clear trend between dose level and toxicity, although abnormal liver transaminase levels appeared more likely to occur within 2 weeks at higher dose levels. All AEs resolved by the end of the study.

The majority of subjects had at least 1 AE, but no increase in the incidence of AEs with increasing dose of TAK-385 was observed. The most common AEs observed across all dose cohorts were bradycardia, hot flush, and headache, and the most common, drug-related AE was hot flush.

A number of cardiac AEs according to Common Terminology Criteria for Adverse Events (CTCAE) were reported, but for these subjects the ECG interpretation was considered to be not clinically significant by the investigator. These cardiac AEs included electrocardiogram QT prolonged (1 AE in Part 1, 4 AEs in Part 2, and 7 AEs in Part 3) and first degree atrioventricular block (2 AEs in Part 1 and 6 AEs in Part 2). Changes in mean QTc interval of approximately 15 to 20 msec were noted before administration on Day 14 (80 to 180 mg QD) in adult male subjects in this study. The QTc changes were independent of drug administration, not correlated to drug levels, and are similar to those observed in surgical and medical castration studies with other

compounds. No major safety concerns were noted in healthy male subjects receiving single (80 to 360 mg) and multiple (20 to 180 mg) doses of TAK-385, and TAK-385 was well tolerated.

Single doses of 80 to 360 mg of TAK-385 administered orally (fasted state) were absorbed rapidly in plasma with median Tmax values ranging from 1.75 to 4.00 hours after administration across the entire dose range. After attaining Cmax, TAK-385 plasma concentrations declined in a multi-exponential manner with a mean T1/2 ranging from 19.1 to 21.7 hours. The mean Cmax and AUC values for TAK-385 generally increased in an approximately dose-proportional manner over the 80 to 360 mg dose range.

When a multiple dose of 20 to 180 mg QD of TAK-385 was administered, the drug was readily absorbed in plasma on Days 1 and 14, and Cmax typically occurred within 1 to 2 hours after dosing. After attaining Cmax, individual PK profiles on Day 14 exhibited a multi-exponential elimination phase with a mean elimination phase T1/2 of approximately 36 to 65 hours at doses of 20 to 180 mg QD. The trough concentration-time data (Day 2, and Days 11 to 14) implied that steady-state conditions were attained within approximately 10 days.

Similarly, the effect of food was studied in 6 male subjects in the crossover period (Part 1). Compared to fasting conditions, the absorption of TAK-385 in plasma decreased and was delayed following a single 180 mg dose taken 30 minutes after the start of a standard FDA high-fat, high-calorie breakfast. Least square mean Cmax and AUC(0-inf) values decreased by approximately 52% and 47%, respectively. Furthermore, median Tmax increased from 1.75 hours to 5.00 hours under fed conditions. When the dose was administered 30 minutes prior to the standardized morning meal (Part 2), systemic exposure to TAK-385 appeared to be reduced to a lesser extent (approximately 28% on average) and no changes in the absorption rate were observed.

In this study, serum LH, FSH, dihydrotestosterone (DHT), and testosterone concentrations were determined following single and multiple oral doses of TAK-385 or placebo for up to 28 days. TAK-385 caused an immediate and effective suppression of gonadotropins (LH, FSH) and testosterone. While no changes were observed in the placebo group, serum testosterone levels were markedly suppressed in all TAK-385 dose groups within the first 3 days of administration. Loading doses of 320/240/160 mg for up to 3 days and doses of 180 mg or greater led to testosterone levels below the conventional castration level within 48 hours. The onset of the testosterone lowering response shortened as the loading dose increased. This phenemon was likely a result of higher TAK-385concentrations in the blood. Similar dose-dependent suppressive effects were observed after a single oral dose. These findings support the principal mechanism of action that, as a GnRH antagonist, TAK-385 competitively binds with the pituitary GnRH receptors.

In administration over 28 days in Part 3 and 4, both 160 mg and 80 mg QD were effective at achieving conventional medical castration levels during the third and fourth weeks of multiple administration. Despite the loading dose regimen, however, the 40-mg QD dose was ineffective in maintaining castration levels between Days 14 and 28. The results at 60 mg QD were intermediate to those of 40 and 80 mg QD and suggested that the likely

minimal, fully effective maintenance dose for medical castration would be 80 mg QD or above [5].

4.1.2.6 Overseas Thorough QTc Study in Healthy Adults ( )

(US) is a double-blind (open-label moxifloxacin), randomized study that evaluated the effect of single doses of TAK-385 on QT/QTc intervals in healthy adults.

[5].

## 4.2 Rationale for the Proposed Study

The results of the phase 1 study conducted in England (TAK-385_C27001) demonstrate the tolerability of multiple doses of TAK-385 (20 to 80 mg) in healthy adult men. Moreover, the plasma concentration of TAK-385 increased as the dose increased, and rose slightly greater than dose proportionality. The blood concentrations of the measured hormones all decreased rapidly with multiple doses of TAK-385 and effective suppression of serum testosterone was sustained throughout the adminsitration period.

Because prostate cancer is a sex-hormone dependent disease, and an antitumor effect is expected as a result of lowering hormone concentrations in the blood through administration of TAK-385, it was decided to conduct a phase 1 study in patients with prostate cancer.

This protocol was prepared in accordance with the Good Clinical Practice (GCP).

# 5.0 STUDY OBJECTIVES AND ENDPOINTS

## 5.1 Objectives

### 5.1.1 Primary Objectives

Part A

To evaluate the tolerability and safety of TAK-385 in hormone treatment-naive patients with non-metastatic prostate cancer.

Part B

To evaluate the safety of TAK-385 in hormone treatment-naive patients with non-metastatic prostate cancer.

### 5.1.2 Secondary Objectives

Part A

To evaluate the PK and the effects on serum testosterone of TAK-385 in hormone treatment-naive patients with non-metastatic prostate cancer.

Part B

To evaluate the change over time in the prostate-specific antigen (PSA) levels and the PK and effects on serum testosterone of TAK-385 in hormone treatment-naive patients with non-metastatic prostate cancer.

## 5.2 Endpoints

### 5.2.1 Primary Endpoints

Part A

Safety: Dose-limiting toxicities (DLTs), AEs, clinical laboratory tests, vital signs, and 12-lead ECGs

Part B

Safety: AEs, clinical laboratory tests, vital signs, and 12-lead ECGs

### 5.2.2 Secondary Endpoints

Part A

PK: Plasma concentrations of unchanged TAK-385

Pharmacodynamics: Serum testosterone concentrations

Part B

Efficacy: PSA levels

PK: Plasma concentrations of unchanged TAK-385

Pharmacodynamics: Serum testosterone concentrations

### 5.2.3 Additional Endpoints

Part A

Efficacy: PSA levels

Pharmacodynamics: LH, FSH, DHT, and sex hormone binding globulin (SHBG) serum concentrations

Part B

Safety: Bone density [6]

Efficacy: Disease progression assessed by PSA, disease progression assessed by imaging

Pharmacodynamics: LH, FSH, DHT, and SHBG serum concentrations

Other: QOL assessments based on the Aging Male's Symptoms (AMS) [7], European Organization for Research and Treatment of Cancer (EORTC)-QLQ-C30 [8, 9, 10], and the Expanded Prostate Cancer Index Composite (EPIC) [11, 12]

# 6.0 STUDY DESIGN AND DESCRIPTION

## 6.1 Study Design

This is a multicenter phase 1, open-label, dose range-finding study to evaluate the tolerability, safety, PK, and pharmacodynamics of TAK-385 alone in hormone treatment-naive Japanese patients with non-metastatic prostate cancer.

This study consists of two parts: Part A, a dose-rising phase, and Part B, an expansion phase. The designs of Part A and Part B are shown in "Study Design and Treatment Schema" (Figure 6.a and Figure 6.b).

In Part A, three to six patients will be enrolled in each cohort. Whether or not the study will proceed to the next cohort or Part B will be determined through assessment of tolerability at the dose in question, based on the incidence of DLT in the evaluation period (treatment initiation to Day 28).

TAK-385 will be taken once a day for 28 days at the doses assigned to each cohort. Cohort 1 will receive a loading dose of 320 mg and a maintenance dose of 80 mg, Cohort 2 will receive a loading dose of 320 mg and a maintenance dose of 120 mg, Cohort 3 will receive a loading dose of 320 mg and a maintenance dose of 160 mg, and Cohort 4 will receive a loading dose of 360 mg and a maintenance dose of 120 mg. The doses will be taken orally at least 30 minutes before breakfast. Patients being switched to a GnRH agonist (eg, leuprorelin) or a GnRH antagonist (eg, degarelix) following the completion of TAK-385 treatment in Part A will first pass through a 1-week observation (no-treatment) period. However, patients whose treatments were discontinued because they met the discontinuation criteria (Section 7.5) during the 28-day treatment period will not have to pass through this observation period.

If tolerability is confirmed in Cohort 2, then the study will proceed to Cohort 3 and Part B simultaneously. The tolerability in Japanese of the maximum dose at which tolerability was found in 28-day multiple dosing in the overseas phase 1 single-/multiple-dose study (TAK-385_C27001) (160 mg) will be evaluated for the purpose of checking the tolerability of dose escalation to 160 mg in Part B as well as the PK. In the overseas phase 1 single-/multiple-dose study (TAK-385_C27001), no findings indicative of safety problems were obtained in multiple dosing for 28 days with 160 mg. However, if tolerability is not confirmed in Cohort 2, then a cohort will be added that will receive a loading dose of TAK-385 320 mg and a maintenance dose of 40 mg.

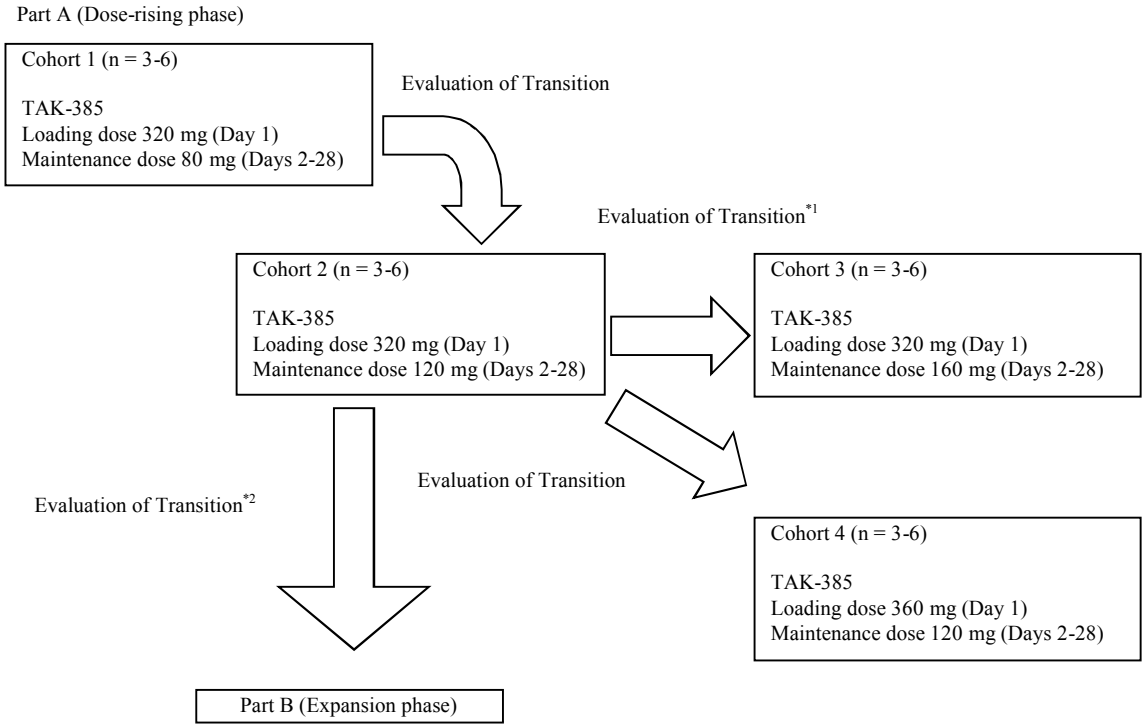
Cohort 4 will be conducted after tolerability is confirmed in Cohort 2. Cohort 4 will be conducted for the purpose of evaluating the tolerability of 360 mg as loading dose in Japanese. 360 mg has been found tolerable in single dosing in the overseas phase 1 single-/multiple-dose study (TAK-385_C27001) [redacted].

In Part B, subjects will be randomized to receive study drug (TAK-385 loading dose of 320 mg and maintenance dose of either 80 mg or 120 mg – equal numbers of subjects will be randomized to 80 mg and 120 mg) once a day orally to evaluate safety. In addition to the safety assessments, efficacy assessments will also be performed according

to the study schedule, and study drug will be administered until the discontinuation criteria (Section 7.5) are met for each individual subject. After completing 48 weeks of treatment, subjects may, at the discretion of the investigator, and depending on the wished of the subhect, continue receiving study drug (for a maximum of 96 weeks), or they may complete the study and be switched to a GnRH agonist (eg, leuprorelin) or a GnHR antagonist (eg, degarelix), starting from the day after the day of the last dose of TAK-385. Subjects withdrawing from the study will not be replaced.

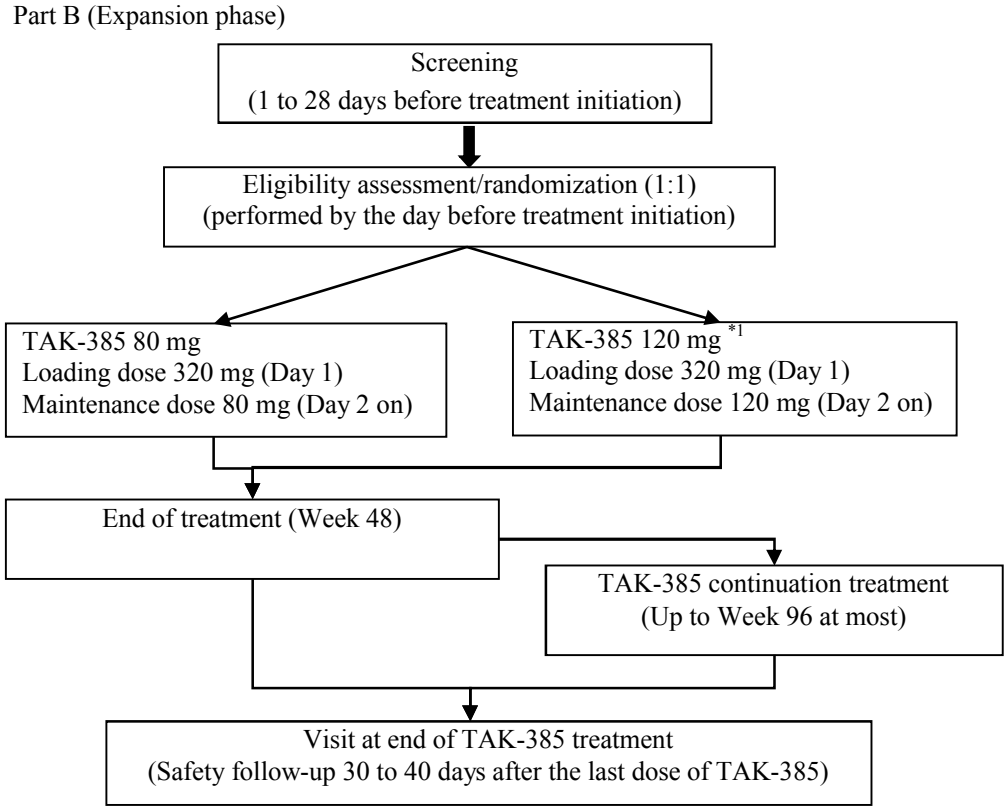
If no problems with tolerability are found in the additional cohort in Part A, then the study will proceed to Part B with a 40 mg group instead of a 120 mg group (TAK-385 loading dose of 320 mg and maintenance dose of 40 mg).

All subjects who receive study drug, whether in Part A or Part B, will undergo safety follow-up 30 to 40 days after the last dose of TAK-385.




*1: If tolerability is not confirmed in Cohort 2, then a cohort will be added which will receive a loading dose of 320 mg and a maintenance dose of 40 mg.
*2: If a cohort is added, and the additional cohort continues to the end and no problems with tolerability are found, then the study will proceed to Part B.

**Figure 6.a. Study Design and Treatment Schema (Part A)**




*1: If a cohort is added in Part A, then in Part B 120 mg group will be replaced to 40 mg group, in which subjects will receive loading dose of 320 mg and maintenance dose of 40 mg.

**Figure 6.b Study Design and Treatment Schema (Part B)**

Figure 6.a and Figure 6.b show an overview of the study schedule. See Appendix A through Appendix E for a more detailed schedule of the study tests, observations, and assessments.

**Table 6.a Study Schedule (Part A)**

| Screening | | Treatment Period<br>DLT Evaluation Period (treatment initiation to Day 28) | | Post-treatment Observation Period | | Safety Follow-up |
|---|---|---|---|---|---|---|
| Outpatient | | Inpatient | Outpatient | Outpatient/Inpatient | | Outpatient |
| Day -28 to Day -1*1 | | Day 1*1 to Day 15 | Day 16 to Day 28*2 | Day 29 to Day 35*2 | ... | 30 to 40 days after the last dose of TAK-385 |
| Screening tests<br>Assessment of eligibility | Admission | Tests/observations<br>Treatment initiation<br>Discharge | Treatment completion<br>Tests/observations | Tests/observations<br>Initiation of other treatment | Observations | Tests/observations |

*1: Day -1 and Day 1 are the day before treatment initiation and the day of treatment initiation, respectively.
*2: Days 27 to 35 are performed either on an outpatient or an inpatient basis.

**Table 6.b Study Schedule (Part B)**

| Screening | Treatment Period | Continuation Treatment Period | Safety Follow-up |
|---|---|---|---|
| Outpatient | | | |
| Days -28 to -1[*1] | Week 1, Day 1[*1] to Week 48, Day 7[*2] | Week 49, Day 1 to Week 96, Day 7[*2] | 30 to 40 days after the last dose of TAK-385 |
| Screening tests<br>Assessment of eligibility, randomization | Tests, observations<br>Treatment initiation<br>Treatment completion | Tests, observations<br>Treatment initiation<br>Treatment completion | Initiation of other treatment<br>Tests, observations |

*1: Day -1 and Day 1 are the day before treatment initiation and the day of treatment initiation, respectively.
*2: Other treatments may be initiated starting on the day after the day of the last dose of TAK-385 (Week 48, Day 8 or Week 96, Day 8).

### 6.1.1 Cohort/Part Advancement Criteria

Whether or not the study will proceed to the next cohort in Part A will be determined by the study sponsor after consulting the study monitoring committee (SMC) and following a comprehensive evaluation of the safety data based on the number of subjects experiencing DLT in each cohort (Table 6.c). Drug will be administered to the subjects in the next cohort after the decision on cohort advancement is made. See the separately prepared written procedures for detailed study advancement criteria.

In each cohort, if no DLT occurs in even 1 of the 3 subjects during the DLT evaluation period (see Section 6.1.2.2), then the dose will be judged tolerable, and the study will proceed to the next cohort. If a DLT occurs in 1 subject in the DLT evaluation period, and additional 3 subjects will be enrolled in this cohort, and DLT will be evaluated in a total of 6 subjects. If DLT occurs in 1 of these 6 subjects, this dose will be judged tolerable, and the study will proceed to the next cohort. If DLT occurs in 2 or more subjects, the study will be stopped, but if it is determined, after consulting the SMC, that this dose is tolerable, then the study will proceed to the next cohort.

Cohort 3, Cohort 4 and Part B will be conducted after tolerability is confirmed in Cohort 2. Whether or not the study will proceed to Part B will be determined by the study sponsor after consulting the SMC based on a comprehensive evaluation of the tolerability and safety data from Cohort 2 of Part A.

If the study cannot proceed from Cohort 2 to Cohort 3 and Part B because of a tolerability problem, the study will proceed to an additional cohort that will receive a TAK-385 loading dose of 320 mg and a maintenance dose of 40 mg. In this case, as well, 3 subjects will be enrolled, and assessed in the same manner as described above. If the study proceeds to the additional cohort, and continues until the treatment of the additional cohort has been completed, and it is confirmed that no problems with tolerability are found, then the study will proceed to Part B.

If DLT occurs in 2 or more subjects in Cohort 3, then whether or not to increase the dose to 160 mg in Part B will be determined in consultation with the SMC.

Because assessment of the MTD is not the objective of this study, additional subjects will not be enrolled if TAK-385 is found to be tolerable in an evaluation of the 3 subjects in Cohort 3 or Cohort 4, nor will additional subjects be enrolled at lower dose levels if TAK-385 is not found to be tolerable at the dose level initially investigated.

**Table 6.c Cohort/Part Advancement Criteria**

| Number of Subjects With DLT (DLT evaluable subjects) | Cohort | Procedure |
|---|---|---|
| 0/3 | 1 | Proceed to Cohort 2 |
| | 2 | Proceed to Cohort 3, Cohort 4 and Part B |
| | 3, 4 | Stop |
| 1/3 | 1 to 4 | Add 3 subjects in the same cohort |
| 2/3 or 3/3 | 1 | Stop |
| | 2 | Add a cohort[*1] |
| | 3, 4 | Stop |
| 1/6 | 1 | Proceed to Cohort 2 |
| | 2 | Proceed to Cohort 3, Cohort 4 and Part B |
| | 3, 4 | Stop |
| ≥ 2/6 | 1 | Stop |
| | 2 | Add a cohort[*1] |
| | 3, 4 | Stop |

*1: TAK-385 loading dose of 320 mg and maintenance dose of 40 mg

**Table 6.d Criteria for Advancing From an Additional Cohort to Part B**

| Number of Subjects With DLT (DLT evaluable subjects) | Procedure |
|---|---|
| 0/3 | Proceed to Part B |
| 1/3 | Add 3 subjects |
| 2/3 or 3/3 | Stop |
| 1/6 | Proceed to Part B |
| ≥ 2/6 | Stop |

### 6.1.2 DLT

#### 6.1.2.1 Definition of DLT

DLTs are defined at treatment-related AEs that occur within the first 28 days of treatment and that meet one of the criteria described below based on CTCAE Version 4.03 (issued June 14, 2010) [13].

1. Grade 3 or higher toxicity

   Clinical laboratory abnormalities meet this criterion if they are found at 2 consecutive time points 7 or more days apart, except for ALT or AST > 3 × upper limit of normal(ULN), total bilirubin > 2 × ULN, or prothrombin time-international normalized ratio (PT-INR) > 1.5 at 2 time points 2 or more days apart.

2. Either of the following ECG findings at 2 time points 7 or more days apart

   - QT/Fridericia corrected QT (QTcF) > 500 msec after treatment initiation
   - QT/QTcF interval prolongation > 60 msec postdose

   The QTcF interval will be calculated using Fridericia's equation ($QT/RR^{0.33}$).

If it is difficult to determine whether or not an event is a DLT and the subject who experienced the event should be included in the DLT analysis set, the sponsor will consult the SMC before making a final decision on whether or not the event is a DLT.

Study treatment will be continued until the end of the 28-day treatment period unless a DLT occurs. If a subject is withdrawn from the study for a reason other than a DLT or if treatment compliance is below 80% (23 doses), the subject will be considered ineligible for inclusion in the DLT analysis set, and replacement subjects will be added in order to obtain 3 or 6 evaluable subjects.

#### 6.1.2.2 DLT Evaluation Period

From treatment initiation until Day 28 in Part A.

#### 6.1.2.3 DLT Evaluable Subjects

Subjects meeting any of the following criteria enrolled in a cohort in Part A.

- Subjects who have taken at least 80% of the doses of TAK-385 (23 doses) during the DLT evaluation period and for whom the DLT evaluation period observations have been completed.
- Subjects who experienced DLTs during the DLT evaluation period.

## 6.2 Rationale for Study Design, Dosage, and Endpoints

(1) Rationale for the target patient population and the study design

The novel GnRH antagonist TAK-385 is expected to compensate for the deficiencies of the GnRH agonists that have been widely used in the treatment of prostate cancer to date, and is being developed as a novel therapeutic medication for prostate cancer. The target patient population for this study was therefore made Japanese patients with prostate cancer.

Because this study will be the first time in Japan that TAK-385 will be administered to patients with prostate cancer, and the safety and efficacy of TAK-385 for the target population have not been sufficiently demonstrated, the TAK-385 treatment period in Part A was set at 28 days. The treatment period would minimize the

inconvenience to subjects with safety concerns or insufficient efficacy. Because TAK-385 will be administered alone to hormone treatment-naive patients with prostate cancer, a placebo would not be used, and that the study would be conducted as an open-label study. It was also decided that if a subject is going to be switched to some other therapy after receiving the last dose of TAK-385 in Part A, then the patient would have to first pass through a 1-week observation (no-treatment) period because of concerns about the safety of the temporary concomitant use of TAK-385 with other therapies. However, subjects meeting the discontinuation criteria (Section 7.5) during the 28-day treatment period would not need to first pass through a 1-week observation period if they need to be switched to some other therapy immediately.

The treatment period in Part B was made 48 weeks long in order to investigate safety and efficacy over a longer period, in light of the fact that the safety and efficacy of TAK-385 in multiple dosing for 28 days will have been confirmed in Part A. If the investigator or sub-investigator determines after 48 weeks that there are no safety problems and that TAK-385 treatment may be continued, then treatment may be continued for up to a total of 96 weeks. Part B was made an open-label phase with randomization to one of two doses the tolerability of which will have been confirmed in Part A. An open-label study design was used because TAK-385 is being administered alone to hormone treatment-naive patient with prostate cancer. In addition, if a subject is going to be switched to some other treatment after the last dose of TAK-385 then, unlike in Part A, and assuming use in the actual clinical setting, it was decided that the other therapy could be initiated without any intervening observation period for confirming the safety of temporary concomitant use with the other therapy.

Furthermore, TAK-385 has been found to be affected by food, and the results that have been obtained suggest that TAK-385 absorption is decreased and delayed when a single dose is taken 30 minutes after food compared to when it is taken in a fasted condition (TAK-385_C27001). It was therefore decided that TAK-385 should be taken at least 30 minutes before breakfast.

Because the company plans to participate in multinational studies in the future, it was decided that Part B would be conducted using the same dosage and administration as that being used in the phase 2 studies being conducted overseas. Because Part B will be conducted using a dosage the tolerability of which will have been confirmed in Cohorts 1 and 2 in Part A, it was decided that Part A Cohort 3 and Part B could be conducted in parallel.

(2) Rationale for loading dose (Part A, Cohort 1)

In a phase 1 study in healthy adult males that was conducted in Europe (TAK-385_C27001), the tolerability of single doses as high as 360 mg and multiple doses as high as 160 mg was confirmed. In order to keep serum testosterone at castration levels and maintain this effect, it was felt that a dose of at least TAK-385 80 mg a day would be necessary as a maintenance dose. In addition, in study

TAK-385_C27001, single doses of TAK-385 180 mg and above reduced serum testosterone levels to castration levels within 48 hours.

[redacted]

Based on these existing data on TAK-385 and on the development plan, it was decided that the loading dose for Cohort 1 in Part A of this study should be 320 mg, a dose that is within the range of doses that have been confirmed to be safe in single dosing, and that can be reliably expected to suppress serum testosterone levels within 48 hours. Given that TAK-385 is going to be used in patients with prostate cancer, the company concluded that it would be necessary to use a dose that could be expected to be effective from the beginning, and that this dose would be tolerated as the loading dose in Japanese. The maintenance dose was set at 80 mg, which can be expected to suppress serum testosterone levels.

(3) Rationale for dosage in Part A, Cohort 4

320 mg or 360 mg may be selected as the loading dose in the planned phase 3 multinational study. Based on this situation, a new cohort, Cohort 4, was added to Part A in Amendment 2 of the study protocol, designed to evaluate the tolerability of loading dose of 360 mg in Japanese patients before joining the phase 3 multinational study. As for the maintenance dose, the same dose as Part A, Cohort 2 (120 mg) was selected, since this dose is expected to keep serum testosterone at castration levels and maintain this effect.

As described in the section above, the tolerability of single doses of 360 mg and multiple doses as high as 160 mg (for 28 days) has been confirmed in a phase 1 study in healthy adult males that was conducted in Europe (TAK-385_C27001). [redacted] Based on the fact that there are no major differences between Japanese and Americans in the pharmacokinetic or pharmacodynamic profiles of TAK-385, and that there are no major differences between the pharmacokinetic profiles obtained in healthy adult men and women, there are no safety concerns in using the loading dose of 360 mg and maintenance dose of 120 mg in Part A, Cohort 4.

(4) Rationale for endpoints

1) Rationale for the primary endpoints

The endpoint in Part A is DLT, in order to confirm the tolerability of TAK-385 in multiple dosing. AEs, clinical laboratory tests, vital signs, and 12-lead ECGs were also made primary endpoints, in order to confirm safety.

In part B, the primary endpoints were made AEs, clinical laboratory tests, vital signs, and 12-lead ECGs, in order to confirm the safety of the use of TAK-385 in multiple dosing for 48 weeks.

2) Rationale for secondary endpoints

In both Part A and Part B, the plasma concentrations of unchanged TAK-385 will be investigated in order to confirm the PK of TAK-385 in multiple dosing. The change in serum testosterone levels over time will also be investigated, in order to confirm the pharmacodynamics. In addition, in Part B, PSA levels will also be evaluated in order to investigate the efficacy of TAK-385 in prostate cancer.

3) Rationale for other endpoints

In Part A, the changes over time in the blood levels of LH, FSH, DHT, and SHBG, which are involved in testosterone synthesis, will be investigated. PSA levels will also be evaluated, in order to preliminarily investigate the efficacy of TAK-385 in prostate cancer.

In Part B, disease progression assessed on the basis of PSA and disease progression assessed on the basis of imaging assessments will be evaluated in accordance with the Prostate Cancer Handling Guidelines, Fourth Edition [16], in order to preliminarily investigate the efficacy of TAK-385 in prostate cancer. In addition, as in Part A, the changes over time in the blood levels of LH, FSH, DHT, and SHBG will also be investigated. Moreover, because androgen-deprivation therapy is known to promote loss of bone mineral density and increase the potential for bone fractures, bone density tests were specified in order to evaluate the effects of TAK-385 on bone mineral density. In nonclinical studies, changes suggesting systemic phospholipidosis have been found in the organs/tissues of animals. Therefore, in order to closely monitor subjects for phospholipidosis, ophthalmology tests were specified, as was assessment of the level of di-docosahexaenoyl (22:6)-bis(monoacylglycero)phosphate (BMP) [14, 15]. Furthermore, in order to evaluate the effects of TAK-385 on quality of life in patients with prostate cancer, quality of life assessments will be performed using the Japanese versions of AMS, EORTC-QLQ-C30, and EPIC, which are widely used in clinical studies overseas.

## 6.3 Premature Termination or Suspension of Study or Investigational Site

### 6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the product, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- The SMC recommends that the study be suspended or terminated.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

### 6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

An investigational site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

### 6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

## 7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All inclusion and exclusion criterial, including test results, need to be checked before study treatment initiation (Part A) or randomization (Part B).

### 7.1 Inclusion Criteria

Subject eligibility will be determined based on the following criteria.

1. Patients judged by the investigator to have the capacity to understand the study and follow the study rules.
2. Patients whose written consent (signature or printed name and personal seal on informed consent form) can be obtained before any study procedures are performed.
3. Japanese male patients 20 or more years of age at the time of informed consent.
4. Patients who, if they have a female partner who could become pregnant, agree to practice appropriate means of contraception from the time of informed consent throughout the entire study treatment period and for 4 months after the last dose of study drug.
5. Patients in stable medical condition, including the absence of acute exacerbations of chronic illnesses, serious infections, or major surgery within 4 weeks (28 days) prior to study treatment initiation.
6. Patients with histologically or cytologically confirmed prostate cancer.
7. Patients whose clinical diagnosis is T1-4 N0 M0, or Tx N0 M0 for patients who have undergone radical prostatectomy.
8. Patients who are considered eligible for hormone therapy for prostate cancer.
9. Patients who have not received hormone therapy (eg, GnRH agonist, GnRH antagonist, steroidal antiandrogen, non-steroidal androgen) for prostate cancer.
10. Patients who have not undergone surgical castration.
11. Patients with serum testosterone at screening > 150 ng/dL.
12. Patients meeting either of the following criteria for PSA at screening.
    - Untreated prostate cancer: PSA at screening > 4.0 ng/mL
    - Treated* prostate cancer: PSA at screening > 0.2 ng/mL

*: Patients who have undergone prostatectomy or either or both of high intensity focused ultrasound therapy or radiotherapy (excluding $^{125}$I-brachytherapy) prior to the start of this study.

13. Eastern Cooperative Oncology Group (ECOG) performance status [17] of 0 or 1 (Appendix G)
14. Body mass index (BMI*) at screening ≥ 18.0 kg/m$^2$

*: BMI will be calculated by the investigational site using the following formula: BMI = Body weight (kg)/(height (m))$^2$

Body weight will be measured in kilograms to the first decimal point, height will be measured in centimeters using integers only, and the results obtained for BMI will be rounded off to the first decimal point.
Example: Weight = 79.2 (kg), height = 176 (cm) = 1.76 (m); BMI = $79.2/1.76^2 = 25.6$ ($kg/m^2$)

## 7.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study.

1. Patients exhibiting symptoms judged related to prostate cancer by the investigator (eg, bone pain, pelvic pain, ureteral obstruction) who urgently require hormone therapy such as GnRH agonist, GnRH antagonist, or combined androgen blockade (CAB)/ maximum androgen blockade (MAB) therapy, chemotherapy, or radiotherapy.
2. Patients who have received 5-alpha reductase inhibitors (except for patients who have been treated for male-pattern alopecias).
3. Patients who have received chemotherapy for prostate cancer (including estramustine).
4. Patients who have received $^{125}$I-brachytherapy.
5. Patients who received radiotherapy (except for $^{125}$I-brachytherapy) within 16 weeks (112 days) before study treatment initiation.
6. Patients who underwent prostatectomy within 16 weeks (112 days before study treatment initiation.
7. Treatment with any investigational compound within the 4 weeks (28 days) prior to the first dose of study drug or ongoing participation in another experimental trial related to the treatment of prostate cancer.
8. Diagnosis or treatment for another systemic malignancy within 2 years before study treatment initiation, or who had received a diagnosis of another malignancy before that and have evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ who have undergone complete resection will not be excluded from the study.
9. Patients taking drugs with moderate to strong CYP3A4 inhibitory or inducing effects, or any medications, supplements, or food products with P-gp inhibitory effects, in the 2 weeks (14 days) prior to study treatment initiation.
10. Patients who have received TAK-385 in a past clinical study.
11. Patients for whom it would be difficult to collect blood from a peripheral vein.
12. Patients with uncontrolled and clinically significant nervous, circulatory, pulmonary, hepatic, renal, metabolic, gastrointestinal, urogenital, or endocrine disorders, or other abnormalities (except for the targeted disease) that could affect study participation or the study results. Also, patients meeting any of criteria a through c below.

a. Patients with uncontrolled diabetes (HbA1c > 8% at screening). However, patients whose HbA1c is brought under control with diabetes medications may be rescreened.

b. Patients with uncontrolled hypertension (systolic blood pressure > 150 mmHg and diastolic blood pressure > 90 mmHg at 2 separate measurements taken no more than 60 minutes apart at screening). Patients whose blood pressure is brought under control by antihypertensive medication may be rescreened.

c. Patients with myocardial infarction, unstable symptomatic ischemic heart disease, arrhythmias of CTCAE Grade > 2, thromboembolism (deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events), or other heart diseases (eg, pericardial effusion, restrictive cardiomyopathy). However, chronic stable atrial fibrillation controlled by stable anticoagulant therapy will be allowed.

13. Patients with bilateral hydronephrosis or bladder neck outlet obstruction.
14. Known hypersensitivity to TAK-385, TAK-385 excipients, or GnRH antagonists.
15. Patients with a past history of gastrointestinal tract treatments (including gastrectomy) or gastrointestinal disease that could affect the drug absorption or tolerability (malabsorption, esophageal reflux, peptic ulcer, erosive esophagitis).
16. Patients positive for hepatitis B surface antigens (HBsAg), hepatitis C virus (HCV) antibodies, human immunodeficiency virus (HIV) antibodies, or serologic test for syphilis, or with life-threatening disease other than cancer, at screening.
17. Clinically relevant ECG abnormalities, or the following ECG abnormalities, at screening.

    a. Q-wave infarction, unless identified 6 or more months prior to TAK-385 treatment initiation

    b. QTcF interval > 450 msec (when calculating the QTc interval, Fridericia's equation [$QT/RR^{0.33}$] will be used)

18. Patients with congenital QT prolongation.
19. Current use of Class 1A or Class 3 antiarrhythmic medications.
20. New York Heart Association [18] Class III or IV heart failure (Appendix H).
21. Patients with clinical laboratory abnormalities suggesting clinically relevant underlying disease, or with any of the following abnormal results, at screening.

    - Serum creatinine ≥ 2.0 mg/dL
    - ALT or AST ≥ 1.5 × ULN for the investigational site
    - Total bilirubin ≥ 2 × ULN for the investigational site
    - Neutrophil count < 1,500/$mm^3$, platelet count < 100,000/μL, hemoglobin < 10.0 g/dL

- Results of heart-related tests (creatine kinase MB [CK-MB] and cardiac troponin T) exceeding the investigational sites reference value.

22. Patients found to have clinical problems on the basis of examination findings, ECG findings, or chest X-ray findings at screening.
23. Patients considered unlikely by investigators to be able to follow the study protocol or considered ineligible for the study by investigators for other reasons.

## 7.3 Prohibited Concomitant Medications, Therapies, and Foods

### 7.3.1 Prohibited Concomitant Medications

The concomitant use of the following medications will be prohibited during the treatment period out of concern for the effects on safety, PK, and pharmacodynamics.
Furthermore, in Part A, the prohibited concomitant medications may not be used until the end of the post-treatment observation period.

- GnRH agonists
- GnRH antagonists
- Steroidal antiandrogens
- Nonsteroidal antiandrogens
- Drugs that include corticosteroids (except for topical drugs)
- Male sex hormone preparations
- Female sex hormone preparations
- 5α reductase inhibitors
- Docetaxel
- Other chemotherapy drugs indicated for prostate cancer
- Drugs with moderately powerful to strongly powerful CYP3A4 inhibitory or inducing effects
- Drugs with P-gp inhibitory effects

### 7.3.2 Prohibited Concomitant Therapies

The following therapies for prostate cancer will be prohibited from study treatment initiation until the end of safety follow-up.

- Surgical castration
- Prostatectomy
- High-intensity focused ultrasound therapy
- Radiotherapy

### 7.3.3 Food

From study treatment initiation and during the treatment period (in Part A, until the end of the post-treatment observation period), the use of nutritional supplements and the consumption of grapefruit and related beverages/foods will be prohibited unless judged necessary by the investigator.

## 7.4 Subject Management

1. Inpatient/outpatient status

   Subjects will be admitted to the investigational site from one day before treatment initiation in each cohort (Day -1) until Day 15 in Part A. As a rule, from Day 16 on, the study will be conducted on an outpatient basis until the safety follow-up. However, from Day 27 on, if a subject lives far from the hospital and it would be difficult for the subject to come to the hospital at the scheduled times, or if the subject desires admission, the study may be conducted on an inpatient basis from Day 27 until Day 35 at the latest. While subjects are inpatients in Part A, they will eat meals (breakfast, lunch, and dinner) at specified times. After being discharged as well, subjects will be instructed to avoid eating or drinking excessively until the end of safety follow-up. When subjects are coming in for visits on an outpatient basis, they will be instructed to be sure to eat dinner on the day before the day of a visit at which a blood sample will be collected for laboratory testing, and they will be instructed to return to the hospital on the following day without eating for blood collection and testing, after which they will receive TAK-385 and then eat breakfast at least 30 minutes later.

   If a subject desires to return home temporarily during the inpatient period, and it would not interfere with study treatment, observations, or tests, then the investigator may allow the subject to return home temporarily, after carefully checking to be sure that the subject's condition is stable, on the basis of the data that have been collected during the study to that point.

   Unless there is a special reason, Part B will as a rule be conducted on an outpatient basis. Subjects will be instructed to observe the scheduled visit times and undergo the examinations and the specified tests. Subjects will also be instructed to inform the investigator promptly if they are not able to come in for a scheduled visit.

2. Study treatment

   Investigators will instruct subjects to take the study drug 30 minutes before breakfast on each day, and to make sure that the time they take the study drug is the same on each day, to the extent possible.

   If a subject forgets to take the study drug 30 minutes before breakfast, the subject should take the drug 30 minutes before lunch on the same day. If a subject forgets to take the study drug both 30 minutes before breakfast and 30 minutes before lunch, the subject should take the study drug 30 minutes before dinner on the same day. It will be explained to subjects that they should not take any study drug that they have forgotten to take on a later day together with the study drug for that day. Subjects will

also be instructed to be sure to note in the patient diary the time they took the study drug as well as whether or not they took the study drug 30 minutes before breakfast.

On scheduled outpatient visit days, subjects will be asked to come to the investigational site in the morning without taking the study drug, and the scheduled tests will be performed.

3. Drinks, etc.

   On days on which study drug is to be taken, subjects will be prohibited from drinking anything from 1 hour before dosing until 30 minutes after, other than one cup of water when they take the study drug.

4. Other

   Investigators will instruct subjects that, if a subjective symptom emerges, it should be reported, along with the date of onset, severity, outcome, and date of outcome, when the subject next visits the investigational site.

   Investigators will instruct subjects not to take any drugs, including over-the-counter drugs, other than the drugs that they are instructed to take, without consulting the investigator in advance.

   Subjects will be instructed that, if they are treated at another medical institution in the time between the treatment period and the safety follow-up, they are to report the background for and nature of said treatment to the investigator, and to inform the medical institution in question that they are participating in a clinical study.

## 7.5 Criteria for Discontinuation or Withdrawal of a Subject

Investigators will enter into the electronic case report form (eCRF) the primary reason for discontinuation or withdrawal of the subject from the study, classified into one of the following categories. See Section 9.1.23 for subjects discontinuing before the study treatment initiation (in the case of Part A) or before randomization (in the case of Part B).

**1. Pretreatment event or adverse event**

This will be considered the primary reason if the subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE; if a serious AE occurs, the subject temporarily stops taking the study drug, and the AE recurs following study treatment resumption, or does not resolve event after 2 weeks of treatment interruption; or if toxicity that is considered DLT occurs in Part A.

- Liver function test abnormalities

  If a LFT abnormality meeting any of the following criteria occurs during study treatment, study drug administration will be discontinued immediately, and appropriate follow-up tests will be performed until the subject's clinical laboratory profile returns to normal, to the level of the first test value obtained after informed

consent (in the case of a PTE), or to baseline (in the case of an AE) (see Section 9.1.8).

- ALT or AST > 3 × ULN; AND total bilirubin > 2 × ULN or PT-INR > 1.5

**2. Major protocol deviation**

This will be considered the primary reason for study withdrawal if it is discovered after the first dose of study treatment (in the case of Part A) or after randomization (in the case of Part B) that the subject does not meet the enrollment criteria specified in the study protocol, or has not followed the study protocol, and that continuing the study would pose an unacceptable risk to the subject's health.

**3. Lost to Follow-up**

This will be considered the primary reason for study withdrawal if a subject fails a study visit and cannot be contacted. In this case, the fact that contact was attempted will be noted in the source documents.

**4. Voluntary withdrawal**

This will be considered the primary reason for withdrawal if the subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE or lack of efficacy should not be recorded in the "voluntary withdrawal" category).

**5. Study termination**

This will be considered the primary reason for withdrawal if the sponsor, IRB, or regulatory authorities decide to terminate the study.

**6. Lack of efficacy**

This will be considered the primary reason for withdrawal if the expected level of efficacy is not obtained because of disease progression assessed by PSA level or evaluation of soft tissue or bone lesions by diagnostic imaging (according to the Prostate Cancer Handling Guidelines, Fourth Edition [16]), or if the decrease in serum testosterone meets any of the following criteria.

1) If, in Part A, serum testosterone does not drop below 50 ng/dL at 2 or more time points at least 7 days apart following treatment initiation, and it is determined as a result that the patient must be switched to some other therapy.
2) If, in Part B, serum testosterone does not drop below 50 ng/dL by 4 weeks after uptitration based on the uptitration criteria (see Section 8.1.3.1).
3) If, in Part B, serum testosterone exceeds 50 ng/dL on 2 consecutive occasions, or on 3 occasions in total, whether consecutive or not, by 9 weeks (57 days) after the start of treatment following uptitration in accordance with the uptitration guidelines (see Section 8.1.3.1).

## 7.6 Procedures for Discontinuation or Withdrawal of a Subject

If a subject meets the criteria described in Section 7.5, the investigator will withdraw the subject from the study. Furthermore, subjects may withdraw from the study without providing a reason at any time during the study. If a subject withdraws from the study, the investigator will enter the primary reason for withdrawal in the eCRF, and will perform all procedures scheduled for the Early Termination Visit.

# 8.0 STUDY DRUG MANAGEMENT

This section contains information regarding all study drugs provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

## 8.1 Study Drug

### 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Investigational Drug

(1) Investigational drug name: TAK-385

(2) Chemical name

*N*-(4-{1-(2,6-Difluorobenzyl)-5-[(dimethylamino)methyl]-1,2,3,4-tetrahydro-3-(6-methoxypyridazin-3-yl)-2,4-dioxothieno[2,3-*d*]pyrimidin-6-yl}phenyl)-*N*'-methoxyurea

(3) Dosage forms and doses

- TAK-385 40 mg tablets: Each tablet contains 40 mg as TAK-385
- TAK-385 80 mg tablets: Each tablet contains 80 mg as TAK-385

There are two types of study drug, described above; both are light red, film-coated tablets.

(4) Packaging and labeling

Each dosage form comes packaged 40 tablets to a bottle. The label clearly states that the drug is for use in a clinical study, and also bears the drug name, protocol number, name and address of the study sponsor (or company that manufactured the drug), manufacturing number, and storage method (Figure 8.a).

For Use in a Clinical Study
TAK-385 40 mg Tablets (or 80 mg Tablets)
For oral administration
Contains 40 tablets
Protocol number: TAK-385/TB-AK160108
Manufacturing number: ●●●●●●●
Storage method: Room temperature (1-30°C)
Expiration date: See the study drug control procedures
Unused study drug and used bottles will be collected by the study sponsor; do not discard.

**Takeda Pharmaceutical Company**
4-1-1 Doshomachi, Chuo-ku, Osaka

**Figure 8.a Sample TAK-385 Bottle Label**

8.1.1.2 Drugs not Provided by the Study Sponsor

No drugs will be provided other than the study drug and drugs such as GnRH agonists and/or GnRH antagonists following the completion (or discontinuation) of TAK-385 administration.

### 8.1.2 Storage

TAK-385 will be stored at room temperature (1-30°C).

Investigational drug must be stored in an appropriate, limited-access, secure place until they are used or until they are returned to the sponsor or a designee for destruction. Investigational drug must be stored under the conditions specified on the label, and must remain in their original containers until dispensed. The daily temperature log of the drug storage area must be maintained every working day.

### 8.1.3 Dose and Regimen

Table 8.a shows the dosage and number of tablets in Part A (by cohort), and Table 8.b shows the dosage and number of tablets in Part B (by treatment group).

**Table 8.a Cohorts, Dosages, and Numbers of Tablets (Part A)**

| Cohort | Dosage/Number of Tablets |
|---|---|
| 1 | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 80 mg (Days 2 to 28): One 80 mg tablet per day |
| 2 | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 120 mg (Days 2 to 28): One 80 mg tablet and one 40 mg tablet per day |
| 3 | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 160 mg (Days 2 to 28): One 80 mg tablet and two 40 mg tablets per day |
| 4 | TAK-385 360 mg (Day 1): Three 80 mg tablets and three 40 mg tablet per day<br>TAK-385 120 mg (Days 2 to 28): One 80 mg tablet and one 40 mg tablet per day |
| Additional cohort[*1] | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 40 mg (Days 2 to 28): One 40 mg tablet per day |

*1: Added if tolerability is not confirmed in Cohort 2

**Table 8.b Treatment Groups, Dosages, and Numbers of Tablets (Part B)**

| Treatment Group | Dosage/Number of Tablets |
|---|---|
| 80 mg | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 80 mg (Day 2 to Week 48[*3]): Two 40 mg tablets per day |
| 120 mg | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 120 mg (Day 2 to Week 48[*3]): One 80 mg tablet and one 40 mg tablet per day |
| 40 mg[*2] | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 40 mg (Day 2 to Week 48[*3]): One 40 mg tablet per day |
| At uptitration | One TAK-385 40 mg tablet per day will be added |

*2: If no problems with tolerability are found in the additional cohort in Part A
*3: Treatment may be continued for up to 96 weeks in total

The specified dose of TAK-385 will be taken once a day orally with 1 cup of water at least 30 minutes before breakfast. Except for when various tests are being performed or an AE occurs, an effort will be made to ensure that subjects rest for 2 hours after receiving the dose.

The investigator or study support staff will check to make sure that all specified study drug has been taken.

#### 8.1.3.1 Criteria for Upward Dose Adjustments

Part A: The dose of TAK-385 will not be increased even if inadequate testosterone suppression occurs (< 50 ng/dL). If after treatment initiation the serum testosterone level does not drop below 50 ng/dL at 2 or more time points separated by at least 7 days and the investigator or sub-investigator determines that the patient needs to be switched to some other treatment, then TAK-385 treatment will be stopped and the patient withdrawn from the study.

Part B: If the following conditions are met, the dose may be adjusted, taking efficacy and safety into consideration. Dose adjustment will be performed when the subject is examined by the investigator or sub-investigator.

If the serum testosterone level in an individual patient exceeds 50 ng/dL at Week 5 (Day 29), Week 9 (Day 57), or Week 13 (Day 85), following review of compliance, a one-time upward dose modification (increment of 40 mg daily) will be allowed. After Week 13, the dose will not be increased even if the serum testosterone level exceeds 50 ng/dL.

The dose will not be increased in the 120 mg group before the DLT evaluations have been completed for Cohort 3 in Part A, or if the dose has not been found to be tolerable. Similarly, if tolerability is not found in Cohort 2 in Part A and a 40 mg group is therefore going to be used instead of a 120 mg group, then the dose in the 80 mg group will not be increased.

#### 8.1.3.2 Criteria for Dose Holds and Dose Reduction

Part A: If a treatment-related AE occurs, or if it would be difficult to continue with TAK-385 treatment, then the dose of TAK-385 will not be reduced, and study treatment will be interrupted if necessary.

Part B: If a treatment-related AE occurs or if it would be difficult to continue with TAK-385 treatment, then study treatment will be interrupted if necessary. Subjects who experience serious AEs requiring study treatment interruption within 12 weeks (84 days) following treatment initiation may have their doses reduced by one dose level – 40 mg – following a 2-week treatment interruption period. If the AE continues even after dose reduction, or the subject's serum testosterone level exceeds 50 ng/dL for 4 to 6 weeks following dose reduction, then TAK-385 treatment will be discontinued so that the subject may receive some other therapy. If a serious AE requiring study treatment interruption occurs on or after Week 13 (Day 85) following treatment initiation, and the subject's treatment has not been interrupted prior to that, then the subject's treatment may be interrupted for 2 weeks and then resumed. However, if the AE recurs following study treatment resumption, or if the AE does not resolve even after 2 weeks of treatment interruption, then the subject will be withdrawn from the study.

Even if the dose has been increased in accordance with Section 8.1.3.1, when reducing the dose, it will be reduced by one dose level. Dose reduction will not be performed for subjects in the 40 mg group. In addition, if the dose is reduced in accordance with this section, then the dose may not be increased as described in Section 8.1.3.1.

Furthermore, if a LFT abnormality is found, it will be handled as shown in Table 8.c.

**Table 8.c Guidelines for Handling Liver Function Test Abnormalities**

| Category | ALT, AST, and Total Bilirubin | Study Drug | ALT and AST Tests | Treatment Interruption | Dose Adjustment |
|---|---|---|---|---|---|
| A | ALT or AST ≥ 1.5 × ULN to < 3 × ULN<br>AND<br>Total bilirubin < 1.5 × ULN | Continue without changing the dose | Perform tests every week for 2 weeks, and then every 2 weeks for 4 weeks until stable[*1] | Not necessary | Not necessary |
| B | ALT or AST ≥ 3 × ULN to < 5 × ULN<br>AND<br>Total bilirubin < 1.5 × ULN | Continue without changing the dose | Perform tests every week, and then every 2 weeks for 4 weeks until stable[*1] | Not necessary | Not necessary |
| C | ALT or AST ≥ 5 × ULN to < 8 × ULN<br>AND<br>Total bilirubin < 1.5 × ULN | Interrupt treatment | Perform 2 tests in the first week, then every week for 2 weeks, and then every 2 weeks until stable[*1] | Interrupt treatment until stable[*1] | Reduce the TAK-385 dose to 40 mg |
| D | ALT or AST ≥ 8 × ULN to < 20 × ULN<br>AND<br>Total bilirubin < 1.5 × ULN | Interrupt treatment | Perform 2 tests a week for the first 2 weeks, and then every 2 weeks until stable[*1] | Interrupt treatment until stable[*1] | Reduce the TAK-385 dose to 40 mg[*2] |
| E | ALT or AST ≥ 3× ULN<br>AND<br>Total bilirubin > 2 × ULN<br>(Hy's law) | Permanently discontinue treatment | Perform 2 tests a week until the test values drop, and then every week until stable[*1] | N/A | N/A |

*1: Stable means ALT and AST both CTCAE Grade 1 (> ULN to 3 × ULN)
*2: The study sponsor should be consulted before resuming treatment.

### 8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.

Serious AEs associated with overdose should be reported according to the procedures outlined in Section 10.2.2.

In the event of a study drug overdose, the investigator will treat the subject symptomatically.

## 8.2 Study Drug Allocation and Prescribing Procedures

In Part A, in order to confirm eligibility for study participation based on the screening tests, the investigator or a person designated by the investigator will contact the registration center by fax. The investigator will prescribe study drug to the subject after confirming that the subject is eligible for the study based on a fax received from the registration center.

In Part B, the investigator or a person designated by the investigator will contact the registration center by fax to confirm the subject's eligibility at the start of the treatment period. After confirming, on the basis of a fax received from the registration center, that the subject is eligible, the investigator will prescribe the subject the study drug for the group to which the subject has been assigned. The investigator or a person designated by the investigator will enter the group to which the subject has been assigned in the eCRF.

Subjects will be assigned a 4-digit number, with the first signifying the Part and Cohort, the second signifying the investigational site, and the last two digits constituting a series number within the cohort at the investigational site. This 4-digit number will be used by the investigational sites to identify the specimens that will be used to assess the PK and pharmacodynamics. These numbers will be noted on the specimen tubes that are provided for measurement, and will be used instead of the subject identification numbers for reporting the measurement results. These numbers will not be replaced by the last 3 digits of the subject identification numbers.

## 8.3 Randomization Code Creation and Storage

The randomization manager (or a person designated by the study sponsor) will prepare a randomization table. The randomization information will be stored in a safe location, and will only be accessible to authorized personnel.

## 8.4 Control and Disposal of Drugs Provided by the Study Sponsor

The study drug controller will receive the written procedures prepared by the study sponsor specifying the handling, storage, and control of study drug, and will appropriately control the drugs provided by the study sponsor in accordance with these written procedures. The investigators will also receive these procedures from the study sponsor. These procedures will describe the procedures that will have to be followed to ensure that the receipt, handling, storage, control, and prescribing of the study drugs provided by the study sponsor, as well as the recovery of unused drugs from subjects and their return to the study sponsor, or their disposal, are carried out appropriately and reliably.

The study drug controlled will promptly return to the study sponsor any unused drugs once the study has been completed at the investigational site in question.

# 9.0 STUDY PLAN

## 9.1 Study Proceduress

The following sections describe the study procedures and data to be collected. In principle, the same investigator will perform examinations and testing, observations, and evaluations of subjects. The Schedule of Study Procedures is shown in Appendix A to Appendix E.

### 9.1.1 Informed Consent

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained from the subject before any protocol-directed procedures are performed.

A unique subject identification number will be assigned to each subject at the time that informed consent is explained. The same subject number will be used throughout the study.

**Informed Consent for Pharmacogenomics**

Informed consent for the storage and banking of the blood sample for pharmacogenomics (PGx) testing in this study must be obtained separately before collection. The provision of consent to collect and analyze the PGx sample is independent of consent to the other aspects of the study.

### 9.1.2 Demographics, Medical History, and Treatment History

Demographic data will include date of birth, sex, and smoking history at screening. The items listed below will be checked with regard to prostate cancer [16]. The findings will be input to the eCRF.

- Date of diagnosis and diagnostic method used
- Gleason classification (pattern 1 to 5 and score) at most recent assessment and date of assessment
- Tissue type and extent of differentiation
- Treatment history (including medication history)
- TNM classification (at time of diagnosis)
- Prostatectomy yes/no, total resection yes/no, date of surgery
- High intensity focused ultrasound yes/no, completion date
- Radiation therapy yes/no, completion date
- History of other therapy yes/no, mode of therapy, start date, completion date

The medical history will include clinically relevant diseases or conditions associated with the targeted disease that disappeared or ended within the past 1 year from the date of

informed consent. If a symptom or disease is still present, it will be considered a comorbidity (concurrent medical condition) (see Section 9.1.18).

Previous therapeutic drugs used (medication history) will include all drugs that were discontinued within 28 days before the date of informed consent and are relevant to the eligibility criteria.

### 9.1.3 Physical Examination

A physical examination will be conducted for the parts of the body listed below (interview, visual inspection, auscultation, palpation, percussion, etc.).

(1) eyes, (2) ears, nose, and throat, (3) cardiovascular system, (4) respiratory organs, (5) digestive organs, (6) skin, (7) extremities, (8) musculoskeletal system, (9) nervous system, (10) lymph nodes, (11) urogenital organs, (12) other

The investigator will evaluate abnormal findings discovered in the pre-administration physical examination for clinical relevance and record the results in the source data. Findings and changes considered to be clinically relevant will be input as PTEs or comorbidities at the proper locations in the source data and eCRF as described in Sections 10.0 and 9.1.18.

### 9.1.4 Weight, Height, and ECOG Performance Status

Weight and height will be measured. Weight will be measured in kilograms to the first decimal place, and height will be measured in centimeters to the closest integer. In addition, the ECOG performance status will be measured in accordance with Appendix G.

### 9.1.5 Vital Signs

Measurement of vital signs will include temperature (axillary), seated blood pressure (systolic and diastolic after resting at least 5 min) and heart rate (bpm). Measurements will be taken after the subject has been sitting for 5 min.

### 9.1.6 Electrocardiogram

A 12-lead ECG will be performed. Measurements will be taken after the subject has been in supine position for 5 min. The investigator (or a specialist at the medical institution) will assess the results by the following categories: Normal range ("Within Normal Limits"), Abnormal but not clinically significant ("Abnormal, Not Clinically Significant "), or Abnormal and clinically significant ("Clinically Significant ").

The following parameters will be transferred from the subject's ECG recording to the eCRF: heart rate, QT interval, PR interval, QRS duration, and RR interval.

In determining the QTc value, Bazett corrected QT (QTcB) and QTcF will be calculated using the Bazett formula ($QT/RR^{0.5}$) and Fridericia formula ($QT/RR^{0.33}$), respectively.

### 9.1.7 Imaging Assessment

CT or MRI (thoracic, abdominal, and pelvic regions) and bone scintigraphy will be performed during screening to verify that there are no distant metastatic lesions. If measurements were taken within 28 days before the start of study drug administration, the results of diagnostic imaging and tests conducted before obtaining informed consent can be used. CT or MRI and bone scintigraphy will also be performed on the days stipulated in the clinical trial schedule (Appendix A to Appendix C) to check for new lesions. Disease progression will be determined by the presence or absence of new lesions based on the items evaluated in diagnostic imaging. Diagnostic imaging will also be performed as needed in Part A if abnormal findings appear in other tests and examinations during administration of the study drug.

### 9.1.8 Clinical Laboratory Tests

Specimens will be handled according to the procedures described in a separate document. A general guideline for the total amount of blood to be collected in this study is shown in Section 9.5.

Samples for clinical laboratory tests will be collected after at least 10 hours of fasting on the days stipulated in the Schedule of Study Procedures (Appendix A to Appendix E). Samples to be collected for each laboratory test are shown in Table 9.a.

**Table 9.a Clinical Laboratory Tests**

| Hematology | Chemistry | Metabolic Panel | Urinalysis |
|---|---|---|---|
| RBC | Total protein | Triglycerides | pH |
| WBC | Albumin | Total cholesterol | Specific gravity |
| Hemoglobin | Glucose | HDL cholesterol | Protein (qualitative) |
| Hematocrit | Creatinine | LDL cholesterol | Glucose (qualitative) |
| Platelet count | BUN | TSH | Occult blood (qualitative) |
| Differential WBC (neutrophils [including absolute count], basophils, eosinophils, lymphocytes, monocytes) | Uric acid | HbA1c | Ketones (qualitative) |
| | Total bilirubin | | Urobilinogen (qualitative) |
| | ALT | | Bilirubin (qualitative) |
| | AST | | |
| | LDH | | |
| | γ-GTP | | |
| | ALP | | |
| | CK(CPK) | | |
| | Na | | |
| | K | | |
| | Cl | | |
| | Ca | | |
| | P | | |
| | PT-INR | | |

**Tests to be conducted when determining eligibility**

(to be performed only when deemed necessary)
HIV test; hepatititis tests including HBsAg and anti-HCV; serologic test for syphilis

The above clinical laboratory tests will be performed at the medical institution. The investigator will evaluate and archive reported clinical laboratory test findings.

When the ALT or AST levels are > 3 × ULN, retesting (at least ALP, ALT, AST, total bilirubin, γ-GTP, and PT-INR) will be performed within 48 to 72 hours (within 7 days at the latest).

(See Section 7.5 for the criteria for the withdrawal from the study. See Section 10.2.3 for the reporting of LFT abnormalities in cases where the ALT or AST level exceeds 3 × ULN, and the total bilirubin level exceeds 2 × ULN or the PT-INR exceeds 1.5.)

The investigator will archive the reference ranges for the clinical laboratory tests, including the history.

All clinically relevant, abnormal laboratory test values will be input in the source data and eCRF of the subject as AEs, etc. All clinically relevant, abnormal laboratory test values verified by retesting will be followed up in all subjects until the abnormal value returns to an acceptable level or there is a sufficient explanation for the observed change.

### 9.1.9 Cardiac Tests

CK-MB and cardiac troponin T will be measured at the institution during screening. These measurements will also be performed as needed when abnormal findings appear in other tests and examinations during administration of the study drug.

### 9.1.10 Tumor Marker

PSA will be measured by a third-party organization according to a separately prepared written procedure. Progression of disease as indicated by PSA (based on the Prostate Cancer Handling Guidelines, 4th Edition [16]) is defined as an increase of at least 25% in the PSA value measured at least 4 weeks after the minimum PSA value measured during the study period (at least 12 weeks if the minimum value was recorded during screening). In such a case, the amount of increase must be at least 2 ng/mL. The date this condition is met will be considered the disease progression date.

### 9.1.11 Collection of Pharmacogenomic Sample

After the start of study drug administration (Part A) or after randomization (Part B), one sample for PGx testing will be collected as early as possible during the administration period. A sample of 5 mL of whole blood for DNA extraction will be collected in an EDTA-treated polypropylene tube from each subject who has given consent. The sample will be sent to the sample storage facility.

Details of collection, handling, and storage of the sample for PGx testing will be carried out according to a separately prepared written procedure.

### 9.1.12 Bone Mineral Density (Part B Only)

Bone mineral density will be measured by dual-energy X-ray absorptiometry (DXA). Throughout the study period the same subject will be measured on the same model of equipment using the same scanning mode. The investigator will input the equipment model, date of measurement, and results for the following measurement parameters into the eCRF.

Measurement sites: Lumbar 2 to 4 (L2 to L4) and hip (femoral neck, femoral trochanteric, femoral intertrochanteric, Ward's triangle, and total)

Measurement parameters: Bone mineral content (BMC, g), bone area (Area, $cm^2$), and bone mineral density (BMD, $g/cm^2$) of L2, L3, and L4, femoral neck, femoral trochanteric, and femoral intertrochanteric regions, and Ward's triangle; and total bone mineral content (BMC, g) (combined), bone area (Area, $cm^2$) (combined), and bone mineral density (BMD $g/cm^2$) (Mean) of L2 to L4 and hip.

### 9.1.13 Ophthalmological Examination (Part B Only)

The examination will be carried out in a darkened room. A slit lamp microscope will be used to examine the anterior of the eye, and the results will be classified as follows: Normal range, Abnormal but not clinically significant, or Abnormal and clinically significant.

### 9.1.14 BMP Concentrations (Part B Only)

BMP will be measured in serum and urine samples by a third-party organization according to a separately prepared written procedure. Sequential BMP testing will not be performed, and the measurements will be summarized after a fixed time period. Measurements will be conducted when there are clinical findings suggesting an association with phospholipidosis or there is a report of an association between comparable GnRH antagonists and phospholipidosis.

### 9.1.15 QOL Assessment (Part B Only)

QOL will be assessed using AMS, EORTC-QLQ-C30, and EPIC scores. After arriving at the hospital each subject will personally fill in the form provided by the sponsor before other tests are conducted and before the study drug is administered. The scoring of QOL will be carried out in the order: AMS, EORTC-QLQ-C30, and EPIC.

### 9.1.16 Concomitant Medications

The term concomitant medication is refers to any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through safety follow-up), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

### 9.1.17 Concomitant Therapies

The term concomitant therapy refers to a medical act carried out for a therapeutic purpose. At each study visit, subjects will be asked whether they have received any therapeutic procedures (performed from signing of informed consent through safety follow-up).

### 9.1.18 Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at screening examinations. The details of the condition (ie., diagnosis) should be recorded in the eCRF.

### 9.1.19 Contraception

Male subjects with female partners who may become pregnant will use a barrier-type contraceptive device (eg, condom and spermicidal cream or jelly) from the time of informed consent until 4 months after the final dose of the study drug. Furthermore, the subject will be instructed not to donate sperm during this time frame.

### 9.1.20 Pregnancy

If the subject's female partner becomes pregnant, the investigator, with the female partner's consent, will inform her attending physician (obstetrician) that the subject was participating in a clinical study when she became pregnant and reveal the details of the study drug.

If a pregnancy is reported for any subject, the investigator, with the subject's consent, will carry out a follow-up investigation until delivery, including premature delivery, and make a report to the sponsor using the designated follow-up form. The investigator will also conduct a postnatal evaluation.

### 9.1.21 Pharmacokinetic Assessments

The plasma concentrations will be measured at each blood sample collection time point (see Appendix D and Appendix E) in accordance with separately prepared written procedures.

The 3 time points for TAK-385 dosing that immediately precede blood sample collection, and the time points for the collection of blood samples for pharmacokinetic assessment, will be entered into the eCRF.

### 9.1.22 Pharmacodynamic Assessments

Serum testosterone, LH, FSH, DHT, and SHBG will be measured by an external measurement facility in accordance with separately prepared written procedures. Serum testosterone will be measured along with other highly sensitive measurements at specified time points (see Appendix B). Detailed information about the treatment and shipment of samples will be provided in the aforementioned written procedures as well.

### 9.1.23 Documentation of Subjects Withdrawing From the Study Prior to Study Treatment Initiation or Prior to Randomization

The principal investigators will be responsible for all subjects who sign informed consent. Investigators will prepare eCRFs for all subjects who withdraw from the study prior to study treatment initiation or randomization.

The primary reason for withdrawal from the study prior to study treatment initiation (in the case of Part A) or prior to randomization (in the case of Part B) will be entered into the eCRF based on the following categories.

- PTE / AE
- Does not meet inclusion criteria or meets exclusion criteria < The reason will be entered. >
- Major deviation from the study protocol
- Follow-up impossible
- Spontaneous withdrawal < The reason will be entered. >
- Entire study discontinued
- Other < The reason will be entered. >

The subject identification numbers of subjects withdrawing from the study will not be reused.

### 9.1.24 Documentation of Study Enrollment/Randomization

In Part A, only subjects who meet all of the inclusion criteria and do not meet any of the exclusion criteria will be enrolled in the treatment period. If a subject cannot proceed to the treatment period, the investigator will enter the primary reason for this in the eCRF.

In Part B, only subjects who meet all of the inclusion criteria and do not meet any of the exclusion criteria will be randomized. If a subject cannot be randomized, the investigator will enter the primary reason for this in the eCRF.

## 9.2 Monitoring Subject Treatment Compliance

During the inpatient period in Part A, the investigator or a person designated by the investigator will give the subject the study drug, confirm that the subject has taken it, and record this in the source documents. For study drug administration following discharge from the investigational site, subjects will be instructed to take the drug appropriately.

On the day of the first dose in Part B, the investigator or a person designated by the investigator will administer the study drug to the subject, confirm that the subject has taken the drug, and record this in the source documents. For study drug administration from Day 2 on, subjects will be instructed to take the drug appropriately.

The day of treatment initiation, the day of treatment completion, the dose, the actions taken with respect to the dose, and the reasons for any changes will be entered in both the source documents and the eCRF.

Subjects will be instructed to bring their study drug (bottles) in with them at each outpatient visit. If it is found that a subject has not complied with the study treatment in the time since the previous visit (eg, if 20% [6 doses] or more of the specified doses have not been taken), then the subject may be withdrawn from the study. If the subject is given instructions about treatment noncompliance, then this will be recorded in the source documents.

## 9.3 Schedule of Observations and Procedures

Appendix A through Appendix E show the schedules for all tests, observations, and assessments. Investigators will perform the tests, observations, and assessments shown below at the specified time points.

### 9.3.1 Screening

Observations and tests will be performed within 28 days prior to the first dose of study drug to confirm subject eligibility for study participation based on the inclusion and exclusion criteria presented in Section 7.0. See Section 9.1.23 for the preparation of records for subjects withdrawing from the study during screening.

The following tests, observations, and assessments will be performed at screening.

- Informed consent
- Demographics, medical history, concurrent medical condition, treatment history
- Physical examination
- Vital signs
- Weight, height, and BMI
- ECOG performance status
- HBsAg, HCV, and HIV antibody and serologic test for syphilis
  If the institutional review board judges it necessary, these tests will be performed only for subjects determined by the investigator to be at high risk for hepatitis B or C or HIV infection.
- 12-lead ECG
- Chest X-ray examination
- Imaging assessments
- Clinical laboratory tests (hematology, chemistry, metabolic panel, and urinalysis)
- Cardiac tests
- Pharmacodynamic assessments (serum testosterone, LH, FSH, DHT, and SHBG)
- Tumor marker (PSA)
- Concomitant medications
- Concomitant therapies
- PTEs

The following tests will be performed only in Part B.

- Ophthalmological examinations
- Bone mineral density
- QOL assessments

### 9.3.2 Study Enrollment/Randomization

In Part A, subjects will be enrolled into each cohort by the day before study treatment initiation on the basis of the results of the aforementioned screening.

In Part B, subjects will be randomized by the day before study treatment initiation on the basis of the results of the aforementioned screening.

Subject who meet all of the inclusion criteria and do not meet any of the exclusion criteria will be enrolled or randomized in accordance with Section 8.2. As described in Section 9.2, subjects will receive their first dose of study drug at the investigational site under the supervision of the investigator or a person designated by the investigator.

### 9.3.3 Day of Study Treatment Initiation

The following tests, observations, and assessments will be performed before study drug is administered on the day of study treatment initiation. If 12-lead ECG or clinical laboratory tests were performed at screening up to 3 days prior to treatment initiation, then they may be used as the tests performed prior to treatment initiation.

- Physical examination
- Vital signs
- Weight
- 12-lead ECG
- Clinical laboratory tests (hematology, chemistry, metabolic panel, and urinalysis)
- Pharmacokinetic assessments

The following tests will be performed only in Part B

- Pharmacodynamic assessments (only serum testosterone by high-sensitivity measurement)
- BMP concentrations
- QOL assessments

### 9.3.4 Study Drug Treatment Period (Except for the Day of Study Treatment Initiation)

During the study treatment period, physical examinations and tests will be performed at scheduled inpatient and outpatient time points. The following tests, observations, and assessments will be performed during the treatment period.

- Physical examination
- Vital signs
- Weight
- ECOG performance status
- 12-lead ECG
- Imaging assessments
- Clinical laboratory tests (hematology, chemistry, metabolic panel, urinalysis)
- Pharmacodynamic assessments (serum testosterone, LH, FSH, DHT, and SHBG)
- Tumor marker (PSA)
- PGx sample collection
- Concomitant medications
- Concomitant therapies
- AEs
- Treatment compliance
- Pharmacokinetic assessments

The following tests will be performed only in Part B

- Ophthalmological examinations
- Bone mineral density
- BMP concentrations
- QOL assessments

### 9.3.5 Post-treatment Observation Period (Performed Only in Part A)

In Part A, the following tests, observations, and assessments will be performed as post-treatment observations for 7 days following the last dose of study drug, and the results will be entered in the eCRF. Even if the subject withdraws from the study during Part A, the same post-treatment observations may be performed, depending on the subject's treatment status. If a subject withdraws from the study, this will be reported to the study sponsor, which will be consulted about what actions should be taken.

- Physical examination
- Pharmacodynamic assessments
- Pharmacokinetic assessments
- Concomitant medications
- Concomitant therapies
- AEs

### 9.3.6 Continuation Treatment Period

In Part B, if a subject continues receiving the study drug after 48 weeks, the following tests, observations, and assessments will be performed every 12, 24, or 48 weeks.

- Physical examination
- Vital signs
- Weight
- ECOG performance status
- 12-lead ECG
- Imaging assessments
- Clinical laboratory tests (hematology, chemistry, metabolic panel, and urinalysis)
- Pharmacodynamic assessments (serum testosterone, LH, FSH, DHT, and SHBG)
- Tumor marker (PSA)
- Concomitant medications
- Concomitant therapies
- AEs
- Treatment compliance
- Bone mineral density
- QOL assessments

### 9.3.7 At Study Withdrawal

If a subject withdraws from the study, the reason for withdrawal will be entered in the source documents and the eCRF, and the following tests, observations, and assessments will be performed within 8 days, including the day of withdrawal. In Part B, if a subject withdraws from the study (before Week 96), these same tests, observations, and assessments will be performed. The status of completion of the study will be entered in the eCRF for all subjects who received study drug in Part A, and for all subjects randomized in Part B. Furthermore, in Part B, if a subject completes 48 weeks of treatment, but does not subsequently continue receiving study drug, then the subject's status of study completion (including the reason treatment was not continued) will be entered in the eCRF.

- Physical examination
- Vital signs
- Weight
- ECOG performance status
- 12-lead ECG

- Imaging assessments
- Clinical laboratory tests (hematology, chemistry, metabolic panel, and urinalysis)
- Pharmacodynamic assessments (serum testosterone, LH, FSH, DHT, and SHBG)
- Tumor marker (PSA)
- Concomitant medications
- Concomitant therapies
- AEs
- Treatment compliance
- Pharmacokinetic assessments (depending on the time of withdrawal)

The following tests will be performed only in Part B.

- Ophthalmological examination (except for subjects who withdraw from the study after advancing to the continuation treatment period)
- Bone mineral density
- BMP concentrations (except for subjects who withdraw from the study after advancing to the treatment continuation period)
- QOL assessments

### 9.3.8 Safety Follow-up

The following tests, observations, and assessments will be performed as safety follow-up 30 to 40 days after the day of the last dose of study drug, and will be the final observations performed.

These same tests, observations, and assessments will be performed 30 to 40 days after the last dose of study drug for subjects who withdraw from the study as well.

The status of study completion will be entered into the eCRF for all subjects who receive study drug in Part A, and for all subjects who are randomized in Part B.

- Physical examination
- Vital signs
- Weight
- ECOG performance status
- 12-lead ECG
- Clinical laboratory tests (hematology, chemistry, metabolic panel, and urinalysis)
- Concomitant medications
- Concomitant therapies
- AEs

The following tests will be performed only in Part B.

- QOL assessments

### 9.3.9 Handling After the End of the Study

Study drug will not be supplied to subjects who have completed the study treatment period and the continuation treatment period (Part B).

## 9.4 Biological Sample Storage and Disposal

The 5 mL samples of whole blood collected for PGx research will be stored frozen at the sample storage facility (Protocol Annex 1).

The storage period will be 20 years from the day the samples for PGx research were initially collected in this study.

During the sample storage period, if a subject wants his samples destroyed, the investigational site will ask, via the study sponsor, and in accordance with the specified procedures, the sample storage facility to destroy the subject's samples. The sample storage facility will destroy the samples in questions in accordance with the procedures, and will inform the investigational site and the study sponsor that the samples have been destroyed. However, if the data that allow the subject to be identified (eg, medical records) have been destroyed once the study has been completed, and it is therefore no longer possible to link the subject to his samples, then the samples will not be destroyed.

Even if the samples can be tied to the subject, if the PGx investigation has already been performed, the remaining samples will be destroyed, but the anonymized results of the PGx investigation will be retained by the study sponsor.

The study sponsor will construct the administrative structure necessary to protect subjects' personal information, and will stipulate in advance criteria for handling sample collection, storage, and disposal, as well as prepare the necessary written procedures.

## 9.5 Blood Sample Volumes and Numbers of Samples Collected

Table 9.b, Table 9.c, and Table 9.d present guidelines for the volumes of blood samples to be collected for each subject.

**Table 9.b Blood Sample Volumes and Numbers of Samples Collected (Part A)**

| Type of Sample | Volume of Blood Collected Per Sample (mL) | Number of Samples (Times) Collected | Total Volume (mL) |
|---|---|---|---|
| Hematology tests | 12 | 7 | **84** |
| Chemistry tests | 9.2 | 7 | **64.4** |
| Metabolic panel tests | 5.6 | 4 | **22.4** |
| Cardiac tests | 4.4 | 1 | **4.4** |
| Tumor marker | 2.0 | 2 | **4** |
| HIV, etc. tests*1 | 5.6 | 1 | **5.6** |
| Pharmacodynamic assessments | 7.0 | 9 | **63** |
| PGx sample collection | 5 | 1 | **5** |
| PK assessments | 3 | 37 | **111** |
| | | **Total Volume of Blood Collected** | **363.8** |

*1: Will be performed only when judged necessary

**Table 9.c Blood Sample Volumes and Numbers of Samples Collected (Part B – Screening Through Week 48, Safety Follow-up)**

| Type of Sample | Volume of Blood Collected Per Sample (mL) | Number of Samples (Times) Collected | Total Volume (mL) |
|---|---|---|---|
| Hematology tests | 12 | 9 | **108** |
| Chemistry tests | 9.2 | 15 | **138** |
| Metabolic panel tests | 5.6 | 8 | **44.8** |
| Cardiac tests | 4.4 | 1 | **4.4** |
| Tumor marker | 2.0 | 9 | **18** |
| BMP concentrations | 2 | 5 | **10** |
| HIV, etc. tests*1 | 5.6 | 1 | **5.6** |
| Pharmacodynamic assessments | 7.0 | 13 | **91** |
| Serum testosterone (high-sensitivity measurement) | 5 | 11 | **55** |
| PGx sample collection | 5 | 1 | **5** |
| PK assessments | 3 | 15 | **45** |
| | | **Total Volume of Blood Collected** | **524.8** |

*1: Will be performed only when judged necessary

**Table 9.d Blood Sample Volumes and Numbers of Samples Collected (Part B – Weeks 49 to 96)**

| Type of Sample | Volume of Blood Collected Per Sample (mL) | Number of Samples (Times) Collected | Total Volume (mL) |
|---|---|---|---|
| Hematology tests | 12 | 4 | **48** |
| Chemistry tests | 9.2 | 4 | **36.8** |
| Metabolic panel | 5.6 | 4 | **22.4** |
| Tumor marker | 2.0 | 4 | **8** |
| Pharmacodynamic assessments | 7.0 | 4 | **28** |
| | | **Total Volume of Blood Collected** | **143.2** |

# 10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

## 10.1 Definition

### 10.1.1 Pretreatment Events

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

### 10.1.2 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug (including study drug); it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

### 10.1.3 Additional Points to Consider for Pretreatment Events and Adverse Events

An untoward findings generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs.)
- Require therapeutic intervention
- Require an invasive diagnostic procedure
- Require discontinuation or a change in dose of study drug or concomitant medication
- Be considered unfavorable by the investigator for any reason.

Diagnosis vs signs and symptoms:
Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) and/or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:
Change in laboratory value or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (ie., if some action or intervention is required, or if the investigators judges the change to be beyond the normal physiological fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation, or monitoring of an abnormality is not considered an intervention.

If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal impairment), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions (disease or symptoms existing before informed consent is obtained):
Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Abnormalities found in initial tests and observations (eg, laboratory tests, ECG, and radiology) after informed consent should NOT be recorded as PTEs unless related to study procedures, except that abnormalities occurring as a result of initial test or observation procedures (such as internal bleeding during blood draw) will be recorded as PTEs in the eCRF. If the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of hypertension").

If a subject has a pre-existing episodic condition (eg, asthma, epilepsy) that increase in frequency or become serious or severe should be recorded as PTEs/AEs. Symptoms that worsen more than expected in subjects with chronic disease (eg, cataracts, rheumatoid arthritis) should also be recorded as PTEs/AEs. Investigators should ensure that the AE term recorded captures the changes in the condition from Baseline (eg, "worsening of XX").

Worsening of PTEs or AEs:
If the subject experiences a worsening or complication of a PTE after starting administration of the study drug or experiences signs/symptoms that occur secondarily to PTEs, the worsening or complication should be recorded appropriately as an AEs in the eCRF. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of XX").

If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE in the eCRF. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of XX").

Underlying disease:
In this study, worsening of the underlying disease will not be handled as an AE. The onset or worsening of symptoms associated with progression of the underlying disease will be handled as an AE.

Planned surgeries or procedures:
Preplanned procedures (surgelies or therapies) that were scheduled prior to signing of informed consent were not considered PTEs or AEs, except that any conditions and events associated with the worsening of pre-existing conditions requiring those procedures to be undertaken on an emergency basis should be captured appropriately as a

PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:
Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):
Insufficient clinical response, efficacy, or pharmacological effect should NOT be recorded as an AE. Investigators must make a distinction between worsening of pre-existing symptoms and lack of efficacy.

Overdose:
Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but overdoses will be recorded on an overdose page of the eCRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

### 10.1.4 Serious Adverse Events

A serious AE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE-THREATENING*.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

* The term "life threatening" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.

**Table 10.a Takeda Medically Significant AE List**

| | |
|---|---|
| Acute respiratory failure/acute respiratory distress syndrome | Hepatic necrosis |
| Torsade de pointes/ventricular fibrillation/ventricular tachycardia | Acute hepatic failure |
| Malignant hypertension | Anaphylactic shock |
| Convulsive seizures (such as convulsions and epilepsy) | Acute renal failure |
| Agranulocytosis | Pulmonary hypertension |
| Aplastic anemia | Pulmonary fibrosis (including interstitial lung disease) |
| Toxic epidermal necrolysis/oculomucocutaenous syndrome (Stevens-Johnson syndrome) | Neuroleptic malignant syndrome/malignant hyperthermia |
| | Spontaneous abortion/stillbirth and fetal death |
| | Confirmed or suspected transmission of infectious agent by drugs |
| | Confirmed or suspected endotoxic shock |

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported by the same procedures as for SAEs (see Sections 10.2.2 and 10.3).

### 10.1.5 Special Interest Adverse Events

A special interest AE (whether serious or not) is one of specific and medical concern specific to the study drug or program. Investigators will monitor subjects on an ongoing basis for such events, and the sponsor will be notified immediately of any that occur. Further investigation may sometimes be necessary to establish assessment of these events. Refer to Section 10.2.1.3 for the methods and deadlines for reports to the sponsor by investigators.

#### 10.1.5.1 Liver Function Test Abnormalities

LFT abnormalities were identified as specific AEs because nonclinical studies in monkeys revealed LFT abnormalities and because clinical studies on oral GnRH antagonists with the same backbone structure as TAK-385 have revealed elevated AST and ALT as common treatment-related AEs.

The management of LFT abnormality AEs is presented in Table 8.c of the protocol. When ALT or AST levels are > 3 × ULN, retesting will be performed within 48 to 72 hours (within 7 days at the latest). As soon as they become aware that ALT or AST levels are > 3 × ULN, investigators will discuss detailed information on affected subjects and other potential causes with the sponsor to review whether the administration of study drug should be discontinued immediately.

If ALT or AST levels are > 3 × ULN and total bilirubin levels are > 2 × ULN or the PT-INR is > 1.5, and investigators conclude that the levels cannot be explained by any factor other that study drug based on the results of retesting, then they will be handled as serious AEs.

When LFT abnormalities correspond to the criteria in Section 7.5, investigators will immediately discontinue administration of study drug and will perform appropriate follow-up.

### 10.1.6 Severity of Pretreatment Events and Adverse Events

The severity of AEs, including laboratory abnormalities, will be determined according to the CTCAE. Events not covered in the CTCAE will be classified and defined as follows.

| | |
|---|---|
| Grade 1 | Mild;[*1] asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated |
| Grade 2 | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[*2] |
| Grade 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limited self care ADL[*3] |
| Grade 4 | Life-threatening consequences; urgent intervention indicated |
| Grade 5 | Death related to AE |

*1: A semi-colon indicates 'or' within the description of the grade.
*2: Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
*3: Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

AEs that undergo a change in severity for the worse will be individually recorded in the eCRF as separate AEs.

Clarification should be made between a serious AE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event, but the event itself may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as "serious." For example, a white blood cell count of 1000 to 2000/$mm^3$ is considered Grade 3 (severe) but may not necessarily be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

### 10.1.7 Causality of Adverse Events

The relationships of each AEs to study drug will be assessed using the following categories:

| | |
|---|---|
| Related | An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concomitant therapies, may also be responsible. |
| Not related | An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concomitant therapies. |

### 10.1.8 Relationship to Study Procedures

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

### 10.1.9 Date of Onset

The date of AE onset (the start date of the AE/PTE) will be determined based on the following criteria.

| AEs | Date of onset |
|---|---|
| Signs, symptoms, disease (diagnosis) | The date on which the subject or investigators first notice the signs or symptoms of an AE will be recorded. |
| Asymptomatic disease | The date on which a diagnostic test is conducted and the diagnosis is confirmed will be recorded.<br>The date on which diagnosis is confirmed will be recorded even when test findings belatedly reveal older findings or when the time of onset can be generally estimated. |
| Worsening of complications or PTEs | The date on which the subject or investigators first notice worsening of signs or symptoms will be recorded. |
| When initial test results after informed consent are normal but subsequent test results are abnormal (PTE)<br>When test results turn abnormal after start of study drug treatment (AEs) | The date on which laboratory abnormalities considered clinically significant are found will be recorded. |
| When test results after informed consent are initially normal but then worsen (PTE)<br>When test results at start of study drug treatment are abnormal and then worsen (AE) | The date of tests on which laboratory profiles reveal clear increases or decreases based on clinical judgment. |

### 10.1.10 Date Resolved

The date resolved (the stop date of the AE/PTE) is the date on which AEs resolve (including resolved with sequelae). When AEs result in death, the date of death will be used. When an AE is recorded as a separate AE in the eCRF due to worsening of severity, the day before the date on which worsening was confirmed will be recorded as the date of resolution. Cases in which resolution cannot be confirmed at the end of the study will be assessed as ongoing.

### 10.1.11 Frequency

When an AE that apparently resolves and occurs repeatedly (such as constipation, diarrhea, and vomiting) is determined by investigators to be a series of occurrences constituting a single event over the period of time from initial onset to ultimate resolution, the incidence will be considered "intermittent." All other cases will be handled as "continuous."

### 10.1.12 Action Taken for Study Drug

Actions taken for study drug will be classified and defined as follows.

| | |
|---|---|
| Drug Withdrawn | A study drug is terminated due to the particular AE (including when subjects themselves decide to discontinue). |
| Dose not Changed | The particular AE did not require any dose change of study drug.<br>Discontinuation of study drug, dose reduction, or dose escalation due to AE other than the AE in question will be handled as "dose not changed."<br>Discontinuation of study drug or dose reduction for reasons other than action taken for the AE, such as subject carelessness, will be handled as "dose not changed." |
| Unknown | When subjects cannot be contacted and the course after the date of onset cannot be ascertained, etc. |
| Not Applicable | When study drug treatment has already been completed or discontinued at the time that the AE occurs |
| Dose Reduced | A reduction in study drug dose as action taken for the AE will be handled as "dose reduced"(the dose cannot be reduced at the subject's discretion) |
| Dose Increased | An escalation in study drug dose as action taken for the AE will be handled as "dose increased"(the dose cannot be escalated at the subject's discretion) |
| Dose Interrupted | A temporary discontinuation (suspension) of study drug as action taken for the AE followed by the resumption of dosing on a later date (including when subjects themselves decide to temporarily discontinue) will be handled as a "dose interrupted." |

### 10.1.13 Outcome

The outcome of AEs will be classified as follows:

| Classification | Criteria |
|---|---|
| Recovered/ Resolved | • Symptoms or findings resolve or recover<br>• Test results normalize or return to levels at baseline (AEs) or to levels at informed consent (PTEs)<br>• When an event is recorded as a separate AE due to worsening severity in the eCRF |
| Recovering/ Resolving | • Severity decreases at least 1 grade<br>• Symptoms and findings are nearly resolved<br>• Test results are improved, but have not normalized or returned to levels at baseline (AEs) or to levels at informed consent (PTEs)<br>• The subject died from a cause other than the particular AE/PTE with the condition remaining “recovering/resolving”. (the date of death does not need to be recorded in such cases) |
| Not Recovered/ Not Resolved | • No change in symptoms, findings, or test results<br>• Symptoms, findings, or test results on last observable day are worse than at onset<br>• Irreversible congenital anomaly/birth defect<br>• The subject died from a cause other than the particular AE/PTE with the particular AE/PTE state remaining “Not recovered/not resolved”. (the date of death does not need to be recorded in such cases) |
| Resolved, with Sequelae | • Occurrence of dysfunction interfering with ADL |

| Classification | Criteria |
|---|---|
| Fatal | • Death immediately related to AEs<br>• "Immediately related" indicates that the AEs caused death or were clearly involved in the death.<br>• Outcomes such as for AEs that are not determined (concluded, assumed) to have been the immediate cause of death in the same subject will not be handled as death.<br>• The date of death will be recorded when the outcome is death. |
| Unknown | • Follow-up of the event cannot be performed as specified in the protocol because of transfer to another hospital, change in residence, or the like |

## 10.2 Procedures

### 10.2.1 Collection and Reporting of Adverse Events

#### 10.2.1.1 Collection Period of Pretreatment Events and Adverse Events

Pretreatment events will be recorded continuously from when informed consent is obtained until the first dose of study drug (Day 1). If it is decided that a subject should be withdrawn before the first dose of study drug, PTEs will be recorded until that point in time.

AEs will be recorded continuously from the start of study drug administration to subjects (Day 1) until the safety follow-up.

#### 10.2.1.2 Reporting of Adverse Events

Investigators will check for subjective symptoms whenever subjects visit. Investigators will ask subjects about AEs that may have occurred since the last visit by asking questions such as "How have you been since the last visit?"

Any subjects who experience a PTE that meets the criteria for seriousness will be followed up by investigators until symptoms resolve or until medically significant laboratory abnormalities return to initial levels after informed consent, or else (in the case of a permanent or irreversible PTE) until the observed change can be satisfactorily explained. No protocol follow-up will be required for PTEs that do not meet the criteria for seriousness, regardless of the causal relationship to study procedure.

Any subjects who experience an AE will be followed up by investigators until symptoms resolve or until medically significant laboratory abnormalities return to initial levels after informed consent, or else (in the case of a permanent or irreversible AE) until the observed change can be satisfactorily explained, regardless of the causal relationship to study drug. All AEs will be recorded in the eCRF. The following information will be documented for each event: event term, start and stop dates, frequency, severity (intensity), causal relationship to study drug (related, not related), action taken on study drug, outcome, causal relationship to study procedures (and procedure considered the cause if causally related), and seriousness.

AEs, and PTEs meeting the criteria for seriousness, will be followed up until the AE/PTEs resolve or until investigators determine that no further follow-up is needed.

#### 10.2.1.3 Reporting of Special Interest Adverse Events

When an AE of special interest that occurs during the period for recording AEs is determined to be medically significant based on the following criteria, investigators will report the event to the sponsor (see attachment for contact information) within 24 hours of the onset of the AE of special interest or within 24 hours after learning of the event from the subject. The principal investigator will also prepare a report of LFT abnormalities (same report form as for SAEs) within 10 business days, and submit it with a signature or printed name and personal seal to the contact identified in the attachment. The "Liver Function Test Abnormality Reporting Checklist (Appendix I)" will be used as reference to assist in the preparation of the report.

The criteria for LFT abnormalities are given below:
• ALT or AST > 3 × ULN

If ALT or AST levels are > 3 × ULN and total bilirubin levels are > 2 × ULN or the PT-INR is > 1.5, and investigators conclude that the levels cannot be explained by any factor other that study drug based on the results of retesting (for procedures, see Section 10.1.5.1), then they will be handled as serious AEs, and information will be recorded and reported by the procedures noted in Section 10.2.2.

AEs of special interest will be recorded as AEs in the eCRF. Related information (such as photographs, results of additional diagnostic tests, and records of consultations with specialists) will also be submitted to the sponsor.

### 10.2.2 Collection and Reporting of Serious Adverse Events

SAEs that occur in the period for recording AEs will be reported by the following procedures. PTEs meeting the criteria for seriousness noted in Section 10.1.4 will be reported by the same procedure as SAEs.

All SAEs that occur from the start of study drug administration in subjects until the safety follow-up will be reported by the principal investigator to the sponsor within 24 hours of confirming or being notified of the event. The initial report of an SAE and all revised or additional information will be recorded in an "SAE Report" to be submitted to the sponsor. Copies of related source documentation on medical treatment of subjects will be submitted to the sponsor as soon as possible. In cases of death, a copy of the autopsy report will be submitted, if possible.

Even after the end of the study, treatment-related SAEs will be reported to the sponsor within 24 hours of confirming or being notified of the event.

SAEs leading to withdrawal from the study or discontinuation of study drug will be recorded in initial or subsequent "SAE Reports" and in the eCRF.

As a general rule, the initial report of an SAE will be faxed to the Safety Information Emergency Response Center using the prescribed "Report of an SAE [Initial Report]" form. After faxing the form, the principal investigator will submit the original to the monitors.

After the initial report of the SAE, the principal investigator will report detailed information to the sponsor within 10 calendar days. As a general rule, the detailed information will be faxed to the Safety Information Emergency Response Center using the prescribed "Report of SAEs (Detailed Information)" form. After faxing the form, the principal investigator will submit the original to the monitors. Any modifications of the contents of the report will be similarly reported.

Safety Information Emergency Response Center (24 hours a day, 365 days a year)
[redacted]
*FAX:* [redacted]
*TEL:* [redacted]

When the Safety Information Emergency Response Center cannot be contacted, the information will, as a general rule, be reported to the monitors using the prescribed "Report of an SAE [Initial Report]" form or "Report of SAEs (Detailed Information)" form.

All SAEs occurring onsite will be reported by the principal investigator to the head of the investigational site by the established procedures in force at the investigational site and to the sponsor in accordance with this protocol.

The expectedness of SAEs will be determined on the basis of the Investigator's Brochure (including information on AEs reported to investigational site).

### 10.2.3 Reporting of Drug-Induced LFT Abnormalities Potentially Leading to Severe Liver Disorders

Investigators will report ALT or AST levels > 3 × ULN to the sponsor and will promptly investigate detailed subject information and potential causes other than study drug (presence or absence of acute viral hepatitis type A or B, or other acute liver diseases, medical history, and complications). Retesting will also be performed (see Section 10.1.5). If ALT or AST levels are > 3 × ULN and total bilirubin levels are > 2 × ULN or the PT-INR is > 1.5, and investigators conclude that the levels cannot be explained by any factor other that study drug, the information will be reported by the same procedure for SAEs (see Section 10.2.1.3).

## 10.3 Follow-up of Serious Adverse Events

If information not reported in the detailed report becomes available at a later date, investigators will record the information on a copy of the SAE report or will prepare a separate document, and one or the other will be submitted to the contact identified in the attachment. Investigational site-related data (such as ECG findings, laboratory findings, summary of report of discharge from hospital, and results of autopsy) will be submitted upon request to the sponsor or the IRB.

Investigators will follow-up all SAEs until they resolve or until the final outcome is determined.

### 10.3.1 Reporting of Serious Adverse Events to Principal Investigators, IRB, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and other SAEs subject to expedited reporting to the regulatory authorities, principal investigators, and the IRBs/head of the investigational site in accordance with the local regulations of the counties in which the study is being conducted. The sponsor or the sponsor's CRO will submit an expedited report of fatal or life-threatening SUSARs within 7 days, and of any other serious events within 15 days, of first learning of or obtaining additional information on the event to the regulatory authorities. The sponsor will also submit an expedited report of other safety issues potentially having a significant effect on the benefit-risk assessment of study drug, continuation of study drug treatment, or continuation of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB.

## 11.0 STUDY SPECIFIC COMMITTEES

A SMC will be established in this study. The principal duties of the SMC will be to decide when cohorts can progress to the next Part or to make the necessary decisions when it is difficult to judge whether or not DLTs have occurred. This is described in detail in separately prepared procedures.

## 12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary [generic term] and the Japanese Drug Dictionary.

### 12.1 Electronic Case Report Form

Completed eCRFs are required for each subject who signs informed consent.

The sponsor or its designee will supply the investigational site with access to the eCRF system. The sponsor will make arrangements to train the investigators and appropriate study support staff in use of the eCRF system. The eCRFs will be used to transmit the information collected during the study to the sponsor and regulatory authorities. The eCRF must be completed in English. Data will be directly recorded onto eCRF.

The following will be recorded as an audit trail when changes or revisions are made in the eCRF: the original and changed/revised information, person making the change or revision, and the date and reasons for the change or revision.

The principal investigator must review the eCRFs for completeness and accuracy, and must electronically sign the appropriate page of the eCRF. The principal investigator bears full responsibility for the accuracy and reliability of all data recorded in the eCRFs.

The following data will not be directly recorded in the eCRF.

1) Tumor marker, BMP concentration, and pharmacodynamic parameters (except for SHBG) measured by an external measurement facilities.
2) Plasma drug concentration results

Investigators will use the eCRF change and revision record (Data Clarification Form) provided by the sponsor when changing or revising recorded entries in the eCRF after the clinical trial database has been locked. The principal investigator must review the data change for accuracy and completeness, and must provide a signature or printed name and personal seal, and the date.

The sponsor or its designee will check the accuracy and completeness of the eCRF when visiting the investigational site. The sponsor or its designee will be permitted to review subject's medical and hospital records related to the study to ensure the accuracy of the eCRFs. Completed eCRFs are the property of the sponsor, and should not be made available in any form to third parties other than regulatory authorities without the written permission of the sponsor.

### 12.2 Record Retention

The principal investigator or head of the investigational site will keep the following records, including the records and study-specific documents specified in Section 12.1. These materials will include the identification log of all participating subjects, medical records, source worksheets, all original signed and dated informed consent forms,

electronic copies of the eCRFs including audit trail, and drug accountability log. The essential relevant documents that are to be archived must also be kept by the principal investigator and head of the investigational site until the day specified as 1) or 2) below, whichever comes later, unless the sponsor requires records to be kept for longer periods of time than this, in which case the head of the investigational site will reach agreement on the retention period and record keeping methods with the sponsor.

1) The day on which marketing approval of the investigational drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2) The day 3 years after the date of early termination or completion of the clinical study.

The principal investigator and head of the investigational site will also keep the essential relevant documents that are to be archived until notified by the sponsor that the records no longer need to be kept.

# 13.0 STATISTICAL METHODS

## 13.1 Statistical and Analytical Plans

Analysts will prepare and finalize the Statistical Analysis Plan before database lock. The Statistical Analysis Plan will describe in detail the definitions of the endpoints and analytical methods in order to meet all study objectives.

Data review will take place before database lock. The accuracy and completeness of the study data, the evaluability of subjects, and the appropriateness of the planned analysis will be assessed during data review.

### 13.1.1 Analysis Sets

Four populations for analysis will be established in this study: the full analysis set, the safety analysis set, the DLT analysis set, and the pharmacokinetic analysis set. The safety analysis set will be defined as all subjects who receive at least 1 dose of any study drug. The DLT analysis set will be defined as all subjects who can be evaluated for DLTs (see Section 6.1.2.3). The analysis sets will be defined in detail in the separately prepared "Rules for Handling Analytical Data."

Before database lock, the sponsor will consult the medical expert as needed to check on the appropriateness of the analysis set definitions and rules for handling the analysis of the case data in the sets, and will finalize the "The Rules for Handling Analytical Data" after deciding how to handle problematic issues not specified at the planning stage.

### 13.1.2 Analysis of Demographics and Other Baseline Characteristics

The primary subject characteristics in the safety analysis set will be tabulated. Descriptive statistics (number of subjects, mean, median, standard deviation, maximum, minimum, and quartiles [same below]) will be calculated for continuous data, and frequency tabulations of discrete data will be prepared.

### 13.1.3 Efficacy Analysis

[Secondary endpoint]

PSA (Part B)

[Analytical method]

The full analysis set will be analyzed as follows.

1) PSA

Descriptive statistics and the two-sided 95% confidence interval of the mean for PSA in Part B will be calculated at each assessment time point specified in the protocol, and the changes over time (individual and mean/SD) will be graphed by dose. The changes from baseline will also be similarly analyzed. Waterfall plots of the change from baseline at Week 13 Day 1 (LOCF) and the change from baseline for the minimum value after the start of study drug treatment will be prepared by dose.

2) Data conversion and handling of missing data

PSA levels below the lower limit of quantification will be handled as the LLOQ. Test data that is not assessed or that is missing, or that is not used per the "Rules for Handling Analytical Data," will be excluded from the analysis of assessment.

[Other endpoints]

- PSA (Part A)
- Disease progression as assessed on the basis of PSA, disease progression as assessed on the basis of image assessment (Part B)

### 13.1.4 Pharmacokinetic Analysis

[Secondary endpoint]

Plasma concentration of unchanged TAK-385

[Analytical method]

The pharmacokinetic profile (such as Cmax and AUC) will be calculated by model-free analysis of the plasma concentration profiles of unchanged TAK-385 in the pharmacokinetic analysis set. Descriptive statistics of each parameter will be calculated by Part and by dose. Descriptive statistics for the plasma concentration of TAK-385 at each blood sampling time point specified in the protocol will also be calculated by dose, and the changes over time (individual and mean) will be graphed by dose. The plasma concentration profiles of TAK-385 will also be analyzed using a compartment model as needed.

### 13.1.5 Pharmacodynamic Analysis

[Secondary endpoint]

Serum testosterone concentration

[Analytical method]

The full analysis set will be analyzed as follows.

1) Serum testosterone concentration

Descriptive statistics and the two-sided 95% confidence interval of the mean for serum testosterone concentration will be calculated by Part and by dose at each assessment time point specified in the protocol, and the changes over time (individual and mean/SD) will be graphed by Part and by dose.

2) Data conversion and handling of missing data

Test parameters below the lower limit of quantification will be handled as the LLOQ. Test data that is not assessed or that is missing, or that is not used per the "Rules for Handling Analytical Data," will be excluded from the analysis of assessment.

[Other endpoints]

Serum concentrations of LH, FSH, DHT, and SHBG

### 13.1.6 Other Analysis

[Other endpoints]

QOL assessment based on AMS, EORTC-QLQ-C30, and EPIC (Part B)

### 13.1.7 Safety Analysis

[Primary endpoints]

DLTs, AEs, clinical laboratory tests, vital signs, and 12-lead ECG

[Analytical methods]

1) Adverse events

The following analysis will be performed for the safety analysis set.

A treatment-emergent adverse event (TEAE) refers to an event that occurs after the start of study drug administration.

The following TEAE will be tabulated by Part and by dose. TEAEs will be coded according to MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT).

- Frequency tabulations of all TEAEs
- Frequency tabulations of treatment-related TEAEs
- Frequency tabulations of all TEAEs by severity
- Frequency tabulations of treatment-related TEAEs by severity
- Frequency tabulations of TEAEs for which the study drug action taken was "treatment discontinuation"
- Frequency tabulations of serious TEAEs
- Frequency tabulations of all TEAEs by time of onset

2) DLT

The following analysis will be performed for the DLT analysis set.

Frequency tabulations of TEAEs determined to be DLTs in Part A will be tabulated by PT and by dose.

3) Clinical laboratory tests, vital signs, and 12-lead ECG

The following analysis will be performed for the safety analysis set.

For continuous data, descriptive statistics for observed values at baseline and at each assessment time point as well as for the change from baseline will be calculated by part and by dose.

Cross tables for the results of the assessment of each test parameter based on discrete data and reference values before and after study drug treatment (such as the determination of

whether results are normal or abnormal, or qualitative laboratory values) will be prepared by part and by dose.

[Other endpoints]

- Bone mineral density

## 13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

## 13.3 Determination of Planned Sample Size

[Part A]

Each cohort will have 3 or 6 subjects, based on the guidelines on the clinical evaluation of antineoplastics.

[Part B]

In order to detect less frequent AEs, 15 subjects per group (total of 30 subjects) were established as the number of cases enabling an approximately 80% chance of detecting AEs characterized by a true incidence of 10%.

# 14.0 QUALITY CONTROL AND QUALITY ASSURANCE

## 14.1 Monitoring of Investigational Site

Monitoring visits to the investigational site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee and by the IRB.

The sponsor or its designee will access the principal investigator's files, medication, medical records of subjects, and records such as the informed consent form to ensure that the study is being properly conducted in compliance with the protocol. They will also confirm the consistency of the eCRFs with related source documents. Investigators and other study support staff members will take the time to accommodate monitors when they visit the investigational site for monitoring purposes.

## 14.2 Protocol Deviations

Investigators may deviate from or modify the protocol without the prior written agreement of the sponsor or prior approval of the IRB for medically unavoidable circumstances, such as to avoid immediate hazards to subjects. On such occasions, the principal investigator will inform the sponsor and head of the investigational site in writing of the details of and reasons for the deviation or change, will keep copies of the notification, and will reach agreement with the sponsor on protocol revisions as needed. If the protocol is to be revised, a draft will be submitted as soon as possible to the head of the investigational site, and the approval of the IRB will be required.

Investigators should document all deviations from the protocol.

## 14.3 Quality Assurance Audits and Regulatory Authority Inspections

The sponsor or designee will audit the investigational site as needed. On such occasions, an auditor designated by the sponsor will contact the investigational site beforehand to schedule the auditing visit. The auditor may ask to visit the facilities where laboratory test samples are kept, the facilities where medication is stored and prepared, and other facilities used during the study. During this study, inspections may also be carried out by regulatory authorities, including overseas agencies (such as the US Food and Drug Administration [FDA] and the UK Medicines and Healthcare Products Regulatory Agency [MHRA]). The sponsor will be notified immediately whenever the investigational site receives a request for an inspection by the regulatory authorities. The principal investigator and head of the investigational site will ensure that the auditor has access to all study-related documentation set forth in Section 14.1.

## 15.0 ETHICAL ASPECTS OF THE STUDY

This trial will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and International Conference on Harmonisation (ICH) Guidelines for GCP. Investigators will conduct the study in accordance with regional regulatory requirements and the "Responsibilities of the Principal Investigator" in Appendix F.

### 15.1 IRB Approval

The IRB must be will be constituted according to the applicable local regulations in regions participating in the study. The sponsor or designee will obtain documentation of the names and affiliations of the IRB members. When IRB members directly participate in the study, documentation that they are not involved in the review and decision-making process must be obtained.

The sponsor or designee will submit related documents to the IRB for review and approval of the protocol. In addition to the study protocol, Investigator's Brochure and copies of the informed consent as well as materials and advertising related to the recruitment of subjects, if needed, and other documents required by local regulations must also be submitted to central or local IRBs for approval. The sponsor or designee will obtain documented approval of the protocol and informed consent form by the IRB before the start of the study (ie., before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will ship drug after confirming the appropriateness of the documented regulations of the investigational site. Until the site receives drug, no protocol activities, including screening may occur.

The investigational site will follow all requirements specified by the IRB. This includes notifications to the IRB regarding protocol amendments, updates to the informed consent form, revisions of materials related to subject recruitment, reports on safety required by local regulatory requirements, periodic reports on the conduct of the study as stipulated by the IRB, and the study completion report. The sponsor or designee will obtain all documented IRB approval of the above and related materials.

Financial compensation paid to subjects should be kept to a level that will not provide undue incentive to participate in the study. Financial relief must be approved by the IRB and sponsor.

PGx analysis of collected and stored samples will perform at the time when the details have been decided. At that time, the sponsor will prepare a PGx protocol, and the protocol will require prior approval of the sponsor.

### 15.2 Patient Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form will describe the

planned and permitted use (either in Japan or abroad: submission to third parties) and disclosure of the personal information and personal medical information of subjects in this study. The informed consent form will further explain the nature of the study, objectives, and of the potential risks and benefits. The informed consent form will also detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care. The principal investigator is responsible for the preparation and contents of the informed consent form, and for obtaining the approval of the IRB. The informed consent form must be approved by the IRB before being used.

The informed consent form must be written in a language fully comprehensible to the prospective subject. Investigators will be responsible for providing subjects with a detailed explanation of the contents of the informed consent form. Information should be provided verbally and in writing by a method deemed suitable by the IRB whenever possible.

Investigators will give subjects (1) a chance to ask questions about the study and (2) enough time to decide whether to participate in the study. Subjects who decide to participate in the study will personally sign and date the informed consent form before participating in the study. Investigators will ask subjects to use a black or blue ball point pen to sign the form using their full legal names. Investigators will also sign and date the informed consent form before the subject can participate in the study.

Investigators will keep the signed original informed consent form. The date on which subjects sign the informed consent form will be recorded by investigators in the medical records of the subjects. Subjects will be given a copy of the signed informed consent form.

If the informed consent form is revised, investigators will again obtain the informed consent of the subjects using the same procedures that were used to obtain initial consent. The date on which informed consent is again obtained will be recorded in the medical records of the subjects, and subjects will be given a copy of the revised informed consent form.

Subjects who have received an explanation of the study based on the informed consent form will be given an explanation of PGx analysis based on the "Informed Consent Form for PGx Analysis in the TAK-385 Study." Specimens for PGx analysis will be obtained from subjects who sign both the informed consent for the study and the informed consent for PGx analysis.

The procedure in Section 9.4 will be followed whenever subjects would prefer their stored samples to be disposed of.

### 15.3 Subject Confidentiality

The sponsor or designee affirm and uphold the principle of the subject’s right to protection against invasion of privacy. Throughout this study, a subject’s source data will only be linked to the sponsor’s clinical study database or documentation via a unique subject identification number. As permitted by all applicable laws and regulations,

limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (such as the FDA, MHRA, and PMDA), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie., the subject's name, address, and other identifier fields not collected on the subject's eCRF).

## 15.4 Publication, Disclosure, and Clinical Trial Registration Policy

### 15.4.1 Publication and Disclosure

The principal investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During the study, except when required by laws or regulations, only the sponsor may disclose study information to other investigators or regulatory authorities. Except where otherwise permitted by the Clinical Study Agreement, any public disclosure of the protocol and study results (including public websites) is the responsibility of the sponsor.

The sponsor may publish any data or information obtained from the study (including data and information provided by the principal investigator) without the consent of the principal investigator.

Investigators need to obtain the prior written permission of the sponsor to publish any information obtained from the study, such as to a professional associations.

### 15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on a public website (JAPIC-CTI) before the start of the clinical trial. The sponsor's contact information will be registered for general access along with the city, state (in the USA), and country where the trial is being conducted as well as subject recruitment status.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the

caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

### 15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on a public website (JAPIC-CTI), as required by applicable laws and/or regulations, regardless of the results.

## 15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or its designee will obtain clinical study insurance against the risk of injury to clinical study subjects.

Refer to the Clinical Study Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or its designee.

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## Appendix A Schedule of Study Procedures (Part A)

| Procedure[a] | Subject consent[b] | Screening | Treatment Period[c] | | | | | | | | | | Post-treatment Observation Period[d] | | | | Withdrawal[e] | SFU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Inpatient[f] | | | | | | | | Outpatient | | | | | | | |
| | | Before treatment initiation D -28 to D -1[g] | D1[h] | D2 | D3 | D7 | D12 | D13 | D14 | D15 | D21 | D28 | D29 | D30 | D31 | D35[i] | | 30 to 40 days after the last dose |
| Allowable visit window | | | 0 | | | | | | | | ± 1 | 0 | 0 | + 3 | + 3 | 0 | + 7 | |
| Confirmation of eligibility | | X | | | | | | | | | | | | | | | | |
| Subject background[j] | | X | | | | | | | | | | | | | | | | |
| Physical examination | | X | X | X | X | X | | | X | | X | X | X | X | X | X | X | X |
| Vital signs[k] | | X | X | | | X | | | X | | X | X | | | | | X | X |
| Weight/height[l] | | X | X | | | X | | | X | | X | X | | | | | X | X |
| ECOG performance status | | X | | | | | | | | | | X | | | | | X | X |
| 12-lead ECG[m] | | X | X[o] | | | | | | X | | | X | | | | | X | X |
| Chest X-ray examination | | X | | | | | | | | | | | | | | | | |
| Imaging assessment[n] | | X | Measure as appropriate | | | | | | | | | | | | | | | |
| Hematology tests | | X | X[o] | | | X | | | X | | X | X | | | | | X | X |
| Blood biochemistry tests | | X | X[o] | | | X | | | X | | X | X | | | | | X | X |
| Blood lipid, sugar, etc. tests | | X | X[o] | | | | | | | | | X | | | | | X | X |
| Urinalysis | | X | X[o] | | | X | | | X | | X | X | | | | | X | X |
| Heart-related tests | | X | Measure as appropriate | | | | | | | | | | | | | | | |
| Pharmacodynamic assessments | | X | | X | X | X | | | X | | X | X | | | X | X | X | |
| Tumor marker | | X | | | | | | | | | | X | | | | | X | |
| Pharmacokinetic assessments[p] | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[q] | |
| PGx sample collection | | | X (during the treatment period) | | | | | | | | | | | | | | | |
| Concomitant medications/ therapies | | Collected from the time of informed consent until 30 to 40 days after the last dose | | | | | | | | | | | | | | | | |
| Adverse events, etc. | PTEs[r] | | Information collected from study treatment initiation until 30 to 40 days after the last dose | | | | | | | | | | | | | | | |
| Study treatment | | | Oral doses once a day at least 30 minutes before breakfast | | | | | | | | | | | | | | | |

Abbreviations: D = Day; ECOG = Eastern Cooperative Oncology Group; PGx = pharmacogenomics; SFU = safety follow-up

a Unless otherwise specified, the assessments will be completed before study drug dosing.
b Except for procedures that are normally part of a physical examination, subjects must sign the informed consent form before any study-related procedures are performed.
c Additional examinations/assessments may be performed at the discretion of the investigator or sub-investigator.
d Days 27 to 35 are performed either on an outpatient or an inpatient basis.
e Unnecessary if the subject withdraws between Day 29 and Day 35.
f Day 1: Day of treatment initiation. As a rule, subjects will not be allowed to leave the investigational site or return home during the inpatient period. However, the investigator or sub-investigator may allow the subject to return home temporarily.
g Day -1: Day before treatment initiation
h Day 1: Day of treatment initiation
i If a subject is going to be switched to a GnRH agonist or a GnRH antagonist, this will be done after PK analysis sample collection and assessments have been completed.
j Including past and current medical history and previous therapeutic medications
k Measurements will be taken after the subject has been sitting down for 5 minutes.
l Height will be measured only at screening.
m 12-lead ECG measurements will be taken after the subject has been lying down for at least 5 minutes.
n Performed at screening only if imaging assessments were not performed within 28 days prior to treatment initiation, or if no usable images are available for the subject.
o Results of tests performed up to 3 days before treatment initiation may be used at the D1 test results.
p See Appendix D for detailed collection times.
q As a rule, blood samples will be collected at subject withdrawal as well, but the blood samples corresponding to the post-treatment observation period will not be necessary.
r Collected from consent acquisition until study treatment initiation.

## Appendix B Schedule of Study Procedures (Part B – Screening to Week 48, SFU)

| Procedure[a] | Informed consent[b] | Screening | Treatment Period[cd] | | | | | | | | | | | | | | | | Withdrawal | SFU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Day | | Before treatment initiation[e] D -28 to D -1[f] | WK 1 D1[h] | WK 1 D2 | WK 1 D4 | WK 2 D1 | WK 3 D1 | WK 5 D1 | WK 9 D1 | WK 13 D1 | WK 17 D1 | WK 21 D1 | WK 25 D1 | WK 29 D1 | WK 33 D1 | WK 37 D1 | WK 41 D1 | WK 45 D1 | WK 49[g] D1 | | 30 to 40 days after the last dose |
| Allowable visit window | | | 0 | 0 | 0 | ±1 | ±1 | ±2 | ±2 | ±2 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±7 | +7 | |
| Confirmation of eligibility | | X | | | | | | | | | | | | | | | | | | | |
| Subject background[i] | | X | | | | | | | | | | | | | | | | | | | |
| Physical examination | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Vital signs[j] | | X | X | | | X | X | X | X | X | | | X | | | | | | X | X | X |
| Weight/height[k] | | X | X | | | X | X | X | X | X | | | X | | | | | | X | X | X |
| ECOG performance status | | X | | | | | | X | | | | | X | | | | | | X | X | X |
| 12-lead ECG[l] | | X | X[n] | | | | X | X | | | | | X | | | | | | X | X | X |
| Chest X-ray examination | | X | | | | | | | | | | | | | | | | | | | |
| Ophthalmology tests | | X | | | | | | | | | | | X | | | | | | X | X | |
| Imaging assessment[m] | | X | | | | | | | | | | | | | | | | | X | X | |
| Bone density (DXA method) | | X | | | | | | | | | | | X | | | | | | X | X | |
| Hematology tests | | X | X[n] | | | | | X | X | X | | | X | | | X | | | X | X | X |
| Blood biochemistry tests | | X | X[n] | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood lipid, sugar, etc. tests | | X | X[n] | | | | | X | X | X | | | X | | | | | | X | X | X |
| Urinalysis | | X | X[n] | | | | | X | X | X | | | X | | | | | | X | X | X |
| Heart-related tests | | X | Measure as appropriate | | | | | | | | | | | | | | | | | | |
| Pharmacodynamic assessments | | X | X[o] | X | X | X[o] | X[o] | X[o] | X[o] | X[o] | X[o] | X[o] | X[o] | | | X[o] | | | X[o] | X | |
| Tumor marker | | X | | | | | | X | X | X | X | X | X | | | X | | | X | X | |
| BMP concentration[p] | | | X | | | | | | X | | | | X | | | X | | | X | X | |
| Pharmacokinetic assessments[q] | | | X | X | X | X | X | X | X | X | X | X | X | | | X | | | X | X[r] | |

| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PGx sample collection | | | X (randomization through the treatment period) | | | | | | | | | | | | | | | | | |
| QOL assessments | | X | X | | | | | X | X | X | | X | X | | | | | X | X | X |
| Concomitant medications/ therapies | | Collected from the time of informed consent until 30 to 40 days after the last dose | | | | | | | | | | | | | | | | | | |
| Adverse events, etc. | | PTEs[s] | Information collected from study treatment initiation until 30 to 40 days after the last dose | | | | | | | | | | | | | | | | | |
| treatment | | | Oral doses once a day at least 30 minutes before breakfast | | | | | | | | | | | | | | | | | |

Abbreviations: WK = Week; D = Day; ECOG = Eastern Cooperative Oncology Group; PGx = pharmacogenomics; QOL = quality of life; SFU = safety follow-up

a Unless otherwise specified, the assessments will be completed before study drug dosing.
b Except for procedures that are normally part of a physical examination, subjects must sign the informed consent form before any study-related procedures are performed.
c Additional examinations/assessments may be performed at the discretion of the investigator or sub-investigator.
d Except for pharmacokinetic assessments, if the assessment and test results can be obtained, then the assessments will be performed before study treatment initiation.
e Randomization will be performed by Day -1 (1 day before treatment initiation)
f Day -1: Day before treatment initiation
g If a subject is going to be switched to a GnRH agonist or a GnRH antagonist, this will be done after PK analysis sample collection and assessments have been completed.
h Day 1: Day of treatment initiation
i Including past and current medical history and previous therapeutic medications
j Measurements will be taken after the subject has been sitting down for 5 minutes.
k Height will be measured only at screening.
l 12-lead ECG measurements will be taken after the subject has been lying down for at least 5 minutes.
m Performed at screening only if imaging assessments were not performed within 28 days prior to treatment initiation, or if no usable images are available for the subject.
n Results of tests performed up to 3 days before treatment initiaion may be used as the D1 test results.
o Blood samples will also be collected for the serum testosterone high sensitivity measurements. However, at WK1D1, only the high-sensitivity measurements will be performed.
p Blood and urine sample collection
q See Appendix E for detailed sample collection times
r As a rule, blood samples will also be collected at withdrawal from the study.
s Information will be collected from consent acquisition until treatment initiation.

## Appendix C Schedule of Study Procedures (Part B – Weeks 49 to 96)

| Procedure[a] | Continuation Treatment Period[b] | | | | | Withdrawal | SFU |
|---|---|---|---|---|---|---|---|
| Scheduled Day | WK49 (WK48) D1 (D8) | WK61 D1 | WK73 D1 | WK85 D1 | WK97[c] D1 | | 30 to 40 days after the last dose |
| Visit Day Allowable Window | ±7 | ±7 | ±7 | ±7 | ±7 | +7 | |
| Physical examination | X | X | X | X | X | X | X |
| Vital signs[d] | X | X | X | X | X | X | X |
| Weight | X | X | X | X | X | X | X |
| ECOG performance status | X | X | X | X | X | X | X |
| 12-lead ECG[e] | X | | X | | X | X | X |
| Imaging assessment | X | | | | X | X | |
| Bone density (DXA method) | X | | X | | X | X | |
| Hematology tests | X | X | X | X | X | X | X |
| Blood biochemistry tests | X | X | X | X | X | X | X |
| Blood lipid, sugar, etc. tests | X | X | X | X | X | X | X |
| Urinalysis | X | X | X | X | X | X | X |
| Pharmacodynamic assessments | X | X | X | X | X | X | |
| Tumor marker | X | X | X | X | X | X | |
| QOL assessments | X | X | X | X | X | X | X |
| Concomitant medications/ therapies | Information collected until 30 to 40 days after the last dose | | | | | | |
| Adverse events, etc. | Information collected until 30 to 40 days after the last dose | | | | | | |
| treatment | Oral doses once a day at least 30 minutes before breakfast[f] | | | | | | |

Abbreviations: WK = Week; D = Day; ECOG = Eastern Cooperative Oncology Group; QOL = quality of life; SFU = safety follow-up

a Unless otherwise specified, the assessments will be completed before study drug dosing.
b Additional examinations/assessments may be performed at the discretion of the investigator or sub-investigator.
c If a subject is going to be switched to a GnRH agonist or a GnRH antagonist, this will be done after PK analysis sample collection and assessments have been completed.
d Measurements will be taken after the subject has been sitting down for 5 minutes.
e Measurements will be taken after the subject has been lying down for 5 minutes.
f Study drug will not be taken at WK97D1.

## Appendix D Schedule of Blood Samples Collection for Pharmacokinetic Analysis (Part A)

| Time Point[a] | Dosing Time Point[b] | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D1 | D2 | D3 | D7 | D12 | D13 | D14 | D15 | D21 | D28 | D29 | D30 | D31 | D35 |
| Before dosing[c] | X | X | X | X | X | X | X | X | X | X | X[d] | X[e] | X[f] | X[g] |
| 0.5 hour (± 10 min) postdose | X | | | | | | X | | | | | | | |
| 1 hour (± 15 min) postdose | X | | | | | | X | | | X | | | | |
| 1.5 hours (± 15 min) postdose | X | | | | | | X | | | | | | | |
| 2 hours (± 20 min) postdose | X | | X | X | | | X | | | X | | | | |
| 4 hours (± 20 min) postdose | X | | | | | | X | | | X | | | | |
| 6 hours (± 30 min) postdose | X | | | | | | X | | | | | | | |
| 8 hours (± 30 min) postdose | X | | | | | | X | | | X | | | | |
| 12 hours (± 1 hour) postdose | X | | | | | | X | | | X | | | | |

Abbreviations: D = day

a If a blood sample is going to be collected on an outpatient basis, then the subject will come in for the visit without taking the study drug.
b As a rule, a blood sample will be collected at discontinuation as well, but the blood sample for the post-treatment observation period will not have to be collected.
c Blood samples for PK analysis will be collected within 1 hour before dosing.
d 24 hours (± 1 hour) after dosing on D28
e 48 hours (± 4 hours) after dosing on D28
f 72 hours (± 4 hours) after dosing on D28
g Collected before starting the next treatment

## Appendix E Schedule of Blood Samples Collection for Pharmacokinetic Analysis (Part B)

| Time Point[a] | Dosing Time Point[b] | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | WK1 | | | WK2 | WK3 | WK5 | WK9 | WK13 | WK17 | WK21 | WK25 | WK37 | WK49 |
| | D1[c] | D2 | D4 | D1 | D1 | D1 | D1 | D1 | D1 | D1 | D1 | D1 | D1 |
| Before dosing[d] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 2 hours postdose (± 20 min) | X | | | | | X | | | | | | | |

Abbreviations: WK = week; D = day

a If a blood sample is going to be collected on an outpatient basis, then the subject will come in for the visit without taking the study drug.
b As a rule, blood samples will be collected at discontinuation as well.
c Blood samples will be collected after the subjects have taken the first dose of study drug at the hospital, and then eaten after an interval of at least 30 minutes, and then after another 2 hours have passed.
d Blood samples for PK analysis will be collected within 1 hour before dosing.

## Appendix F Responsibilities of Principal Investigator

1. Conduct the appropriate study in accordance with the protocol and GCP considering the rights, safety and wellbeing of human subjects.
2. When a part of the important activities related to the study are delegated to the sub-investigator or the study support staff, prepare the lists of activities to be delegated and responsible personnel, submit the lists to the head of the site in advance to get them accepted.
3. Prepare a written informed consent form and other written information, and update as appropriate.
4. Confirm the contents of the Clinical Study Agreement.
5. Provide necessary information on the protocol, drugs and responsibilities of individual personnel to the sub-investigator and study support staff, and provide guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide the explanation of the study in writing and obtain the written consent.
7. Assume responsibility for all the medical judgement related to the study.
8. Ensure in collaboration with the head of the site that sufficient information on all clinicaly significant advesrse events related to the study are provided to subjects throughout and beyond the period when subjects participate in the study.
9. If a subject consult other medical institution or other department, notify the physician of the medical institution or department of the subject's participation in the study, as well as the end and termination of the study in writing, and document such records.
10. In case of urgent report of a SAE, immediately notify the head of the site and the sponsor in writing.
11. Prepare correct and complete eCRFs, and submit them to the sponsor with electronic signature.
12. Check and confirm the contents of eCRFs prepared by the sub-investigator or transcribed from the souce data by the study support staff, and submit them to the sponsor with electronic signature.
13. Discuss any proposal from the sponsor including update of the protocol.
14. Notify the head of the site of the end of the study in writing.

## Appendix G ECOG Performance Status

| Score | Activity Level |
|---|---|
| 0 | Normal activity. Fully active, able to carry on all predisease performance without restriction. |
| 1 | Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work). |
| 2 | In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead. |

## Appendix H New York Heart Association (NYHA) Functional Classification

| Class | Patient Symptoms |
|---|---|
| I | Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain. |
| II | Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain. |
| III | Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain. |
| IV | Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased. |

## Appendix I Liver Function Test Abnormality Reporting Checklist

**AS MUCH INFORMATION AS POSSIBLE WILL BE OBTAINED ABOUT THE FOLLOWING PARAMETERS**

**RELATED MEDICAL HISTORY/SYMPTOMS**

☐ Viral hepatitis
☐ Auto-immune disorders
☐ Alcohol use
☐ Biliary disorders
☐ Heart disorders, particularly right heart failure or hypotension
☐ Recent viral diseases
☐ Recent travel
☐ Blood transfusions
☐ Allergies
☐ Recent anesthesia/surgical procedures
☐ Drug abuse
☐ Exposure to toxins
☐ Recent tattoos
☐ Family history of liver disease

**EVENT INFORMATION**

☐ Signs and symptoms

**NOTEWORTHY CLINICAL TEST DATA AND TEST RESULTS**

☐ Hepatic enzymes (ALT, AST, total bilirubin, ALP, GGT)
☐ Coagulation system parameters
☐ Albumin
☐ Virus serum tests
☐ Auto-immune markers
☐ Liver imaging tests (ultrasound, CT, MRI)
☐ Endoscopic retrograde cholangiopancreatography (ERCP)
☐ Liver biopsy
☐ Eosinophil count

## Appendix J Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Incorporating Amendment No.2.

**Page 8, Section 2.0 STUDY SUMMARY**

**Existing Text**

**Study Design:**

•••

Cohort 1 will receive a loading dose of 320 mg and a maintenance dose of 80 mg, Cohort 2 will receive a loading dose of 320 mg and a maintenance dose of 120 mg, *and* Cohort 3 will receive a loading dose of 320 mg and a maintenance dose of 160 mg.

•••

**Revised Text**

**Study Design:**

•••

Cohort 1 will receive a loading dose of 320 mg and a maintenance dose of 80 mg, Cohort 2 will receive a loading dose of 320 mg and a maintenance dose of 120 mg, Cohort 3 will receive a loading dose of 320 mg and a maintenance dose of 160 mg, **and Cohort 4 will receive a loading dose of 360 mg and a maintenance dose of 120 mg**.

•••

**Rationale for Amendment**

Addition of Cohort 4 (loading dose of 360 mg and maintenance dose of 120 mg) to Part A for the purpose of evaluating the tolerability of 360 mg as loading dose in Japanese.

**Page 9, Section 2.0 STUDY SUMMARY**

**Existing Text**

**Numbers of Subjects:**

Part A: 3 to 6 subjects in each cohort (3 to *18* subjects in total)

Part B: 15 subjects in each group (30 subjects in total)

**Revised Text**

**Numbers of Subjects:**

Part A: 3 to 6 subjects in each cohort (3 to **24** subjects in total)

Part B: 15 subjects in each group (30 subjects in total)

**Rationale for Amendment**

Change based on the addition of Part A, Cohort 4.

**Page 9, Section 2.0 STUDY SUMMARY**

**Existing Text**

**Dosage:**

Part A

Cohort 1: Loading dose of 320 mg and maintenance dose of 80 mg

Cohort 2: Loading dose of 320 mg and maintenance dose of 120 mg

Cohort 3: Loading dose of 320 mg and maintenance dose of 160 mg

(Additional cohort: Loading dose of 320 mg and maintenance dose of 40 mg)

**Revised Text**

**Dosage:**

Part A

Cohort 1: Loading dose of 320 mg and maintenance dose of 80 mg

Cohort 2: Loading dose of 320 mg and maintenance dose of 120 mg

Cohort 3: Loading dose of 320 mg and maintenance dose of 160 mg

**Cohort 4: Loading dose of 360 mg and maintenance dose of 120 mg**

(Additional cohort: Loading dose of 320 mg and maintenance dose of 40 mg)

**Rationale for Amendment**

Change based on the addition of Part A, Cohort 4.

**Page 25, Section 4.1.2 Clinical Studies**

**Existing Text**

Not applicable

**Revised Text**

**4.1.2.6 Overseas Thorough QTc Study in Healthy Adults ( )**

**is a double-blind (open-label moxifloxacin), randomized study that evaluated the effect of single doses of TAK-385 on QT/QTc intervals in healthy adults.**

[redacted] **[5]**.

**Rationale for Amendment**

Insertion of results from a completed clinical study.

**Page 28, Section 6.1 Study Design**

**Existing Text**

**•••**

TAK-385 will be taken once a day for 28 days at the doses assigned to each cohort. Cohort 1 will receive a loading dose of 320 mg and a maintenance dose of 80 mg, Cohort 2 will receive a loading dose of 320 mg and a maintenance dose of 120 mg, *and* Cohort 3 will receive a loading dose of 320 mg and a maintenance dose of 160 mg. The doses will be taken orally at least 30 minutes before breakfast.

**•••**

However, if tolerability is not confirmed in Cohort 2, then a cohort will be added that will receive a loading dose of TAK-385 320 mg and a maintenance dose of 40 mg.

In Part B, subjects will be randomized to receive study drug (TAK-385 loading dose of 320 mg and maintenance dose of either 80 mg or 120 mg – equal numbers of subjects will be randomized to 80 mg and 120 mg) once a day orally to evaluate safety.

**•••**

**Revised Text**

**•••**

TAK-385 will be taken once a day for 28 days at the doses assigned to each cohort. Cohort 1 will receive a loading dose of 320 mg and a maintenance dose of 80 mg, Cohort 2 will receive a loading dose of 320 mg and a maintenance dose of 120 mg, Cohort 3 will receive a loading dose of 320 mg and a maintenance dose of 160 mg, **and Cohort 4 will receive a loading dose of 360 mg and a maintenance dose of 120 mg.** The doses will be taken orally at least 30 minutes before breakfast.

**•••**

However, if tolerability is not confirmed in Cohort 2, then a cohort will be added that will receive a loading dose of TAK-385 320 mg and a maintenance dose of 40 mg.

**Cohort 4 will be conducted after tolerability is confirmed in Cohort 2. Cohort 4 will be conducted for the purpose of evaluating the tolerability of 360 mg as loading dose**

**in Japanese. 360 mg has been found tolerable in single dosing in the overseas phase 1 single-/multiple-dose study (TAK-385_C27001)** [redacted]

In Part B, subjects will be randomized to receive study drug (TAK-385 loading dose of 320 mg and maintenance dose of either 80 mg or 120 mg – equal numbers of subjects will be randomized to 80 mg and 120 mg) once a day orally to evaluate safety.

•••

**Rationale for Amendment**

Change based on the addition of Part A, Cohort 4.

**Page 29, Section 6.1 Study Design**

**Existing Text**

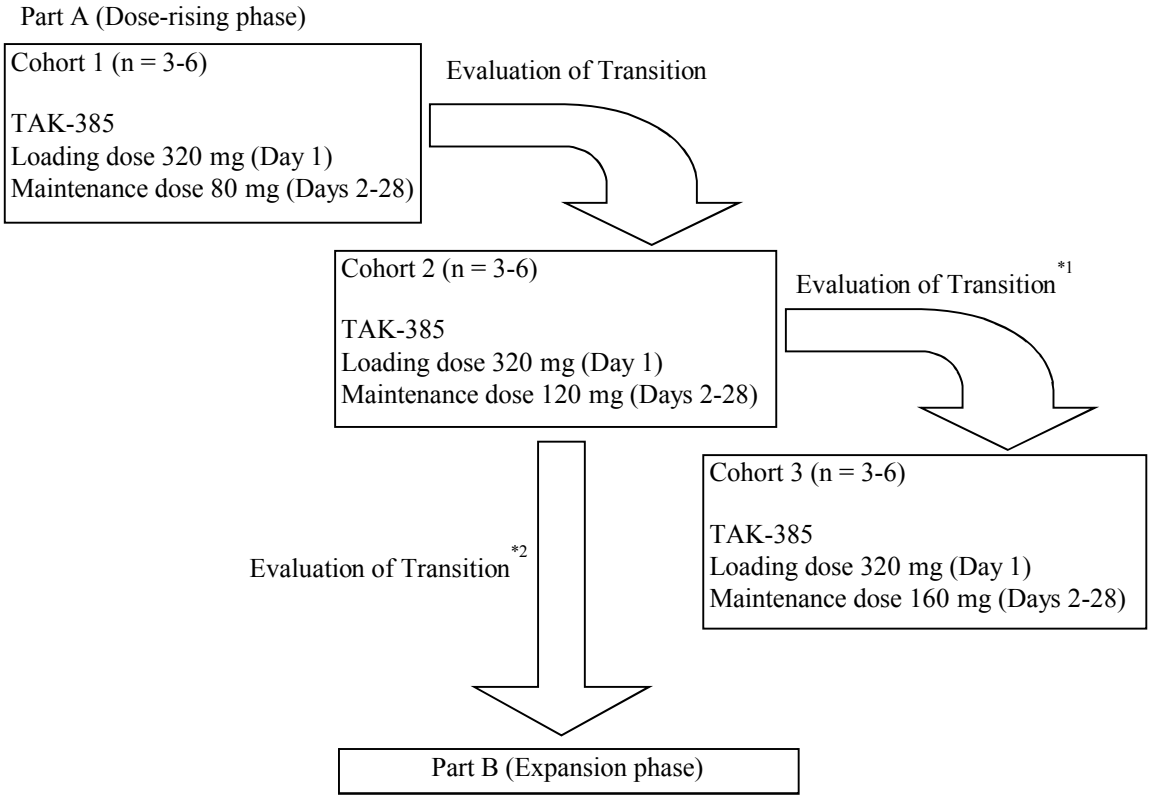


Figure 6.a. Study Design and Treatment Schema (Part A)

## Revised Text

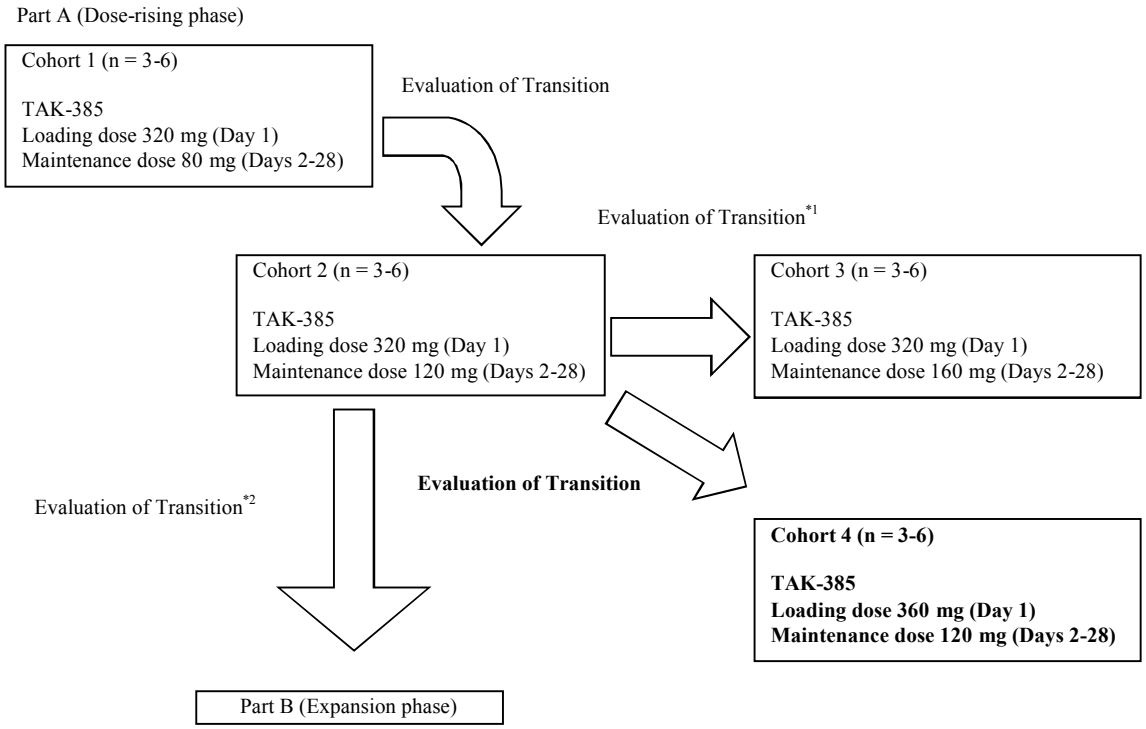


Figure 6.a. Study Design and Treatment Schema (Part A)

### Rationale for Amendment

Change based on the addition of Part A, Cohort 4.

## Page 30, Section 6.1 Study Design

### Existing Text

Figure 6.a and Figure 6.b show an overview of the study schedule. See Appendix A through *Appendix D* for a more detailed schedule of the study tests, observations, and assessments.

### Revised Text

Figure 6.a and Figure 6.b show an overview of the study schedule. See Appendix A through **Appendix E** for a more detailed schedule of the study tests, observations, and assessments.

### Rationale for Amendment

Correction of typographical error.

**Page 31 to 32, Section 6.1.1 Cohort/Part Advancement Criteria**

**Existing Text**

•••

Whether or not the study will proceed to *Cohort 3 and Part B* will be determined by the study sponsor after consulting the SMC based on a comprehensive evaluation of the tolerability and safety data from Cohort 2 of Part A.

•••

Because assessment of the MTD is not the objective of this study, additional subjects will not be enrolled if TAK-385 is found to be tolerable in an evaluation of the 3 subjects in *Cohort 3*, nor will additional subjects be enrolled at lower dose levels if TAK-385 is not found to be tolerable at the dose level initially investigated.

**Revised Text**

•••

**Cohort 3, Cohort 4 and Part B will be conducted after tolerability is confirmed in Cohort 2.** Whether or not the study will proceed to Part B will be determined by the study sponsor after consulting the SMC based on a comprehensive evaluation of the tolerability and safety data from Cohort 2 of Part A.

•••

Because assessment of the MTD is not the objective of this study, additional subjects will not be enrolled if TAK-385 is found to be tolerable in an evaluation of the 3 subjects in **Cohort 3 or Cohort 4**, nor will additional subjects be enrolled at lower dose levels if TAK-385 is not found to be tolerable at the dose level initially investigated.

**Rationale for Amendment**

Change based on the addition of Part A, Cohort 4.

## Page 32, Section 6.1.1 Cohort/Part Advancement Criteria

### Existing Text

Table 6.c Cohort/Part Advancement Criteria

| Number of Subjects With DLT (DLT evaluable subjects) | Cohort | Procedure |
|---|---|---|
| 0/3 | 1 | Proceed to Cohort 2 |
| | 2 | *Proceed to Cohort 3 and Part B* |
| | *3* | Stop |
| 1/3 | *1 to 3* | Add 3 subjects in the same cohort |
| 2/3 or 3/3 | 1 | Stop |
| | 2 | Add a cohort[*1] |
| | *3* | Stop |
| 1/6 | 1 | Proceed to Cohort 2 |
| | 2 | *Proceed to Cohort 3 and Part B* |
| | *3* | Stop |
| ≥ 2/6 | 1 | Stop |
| | 2 | Add a cohort[*1] |
| | *3* | Stop |

### Revised Text

Table 6.c Cohort/Part Advancement Criteria

| Number of Subjects With DLT (DLT evaluable subjects) | Cohort | Procedure |
|---|---|---|
| 0/3 | 1 | Proceed to Cohort 2 |
| | 2 | **Proceed to Cohort 3, Cohort 4 and Part B** |
| | **3, 4** | Stop |
| 1/3 | **1 to 4** | Add 3 subjects in the same cohort |
| 2/3 or 3/3 | 1 | Stop |
| | 2 | Add a cohort[*1] |
| | **3, 4** | Stop |
| 1/6 | 1 | Proceed to Cohort 2 |
| | 2 | **Proceed to Cohort 3, Cohort 4 and Part B** |
| | **3, 4** | Stop |
| ≥ 2/6 | 1 | Stop |
| | 2 | Add a cohort[*1] |
| | **3, 4** | Stop |

### Rationale for Amendment

Change based on the addition of Part A, Cohort 4.

**Page 34, Section 6.2 Rationale for Study Design, Dosage, and Endpoints**

**Existing Text**

(1) Rationale for the target patient population and the study design

•••

The treatment period in Part B was made 48 weeks long in order to investigate safety and efficacy over a longer period, in light of the fact that the safety and efficacy of TAK-385 in multiple dosing for 28 days will have been confirmed in Part A. If the investigator determines after 48 weeks that there are no safety problems and that TAK-385 treatment may be continued, then treatment may be continued for up to a total of 96 weeks.

•••

**Revised Text**

(1) Rationale for the target patient population and the study design

•••

The treatment period in Part B was made 48 weeks long in order to investigate safety and efficacy over a longer period, in light of the fact that the safety and efficacy of TAK-385 in multiple dosing for 28 days will have been confirmed in Part A. If the investigator **or sub-investigator** determines after 48 weeks that there are no safety problems and that TAK-385 treatment may be continued, then treatment may be continued for up to a total of 96 weeks.

•••

**Rationale for Amendment**

Revised to better fit the actual situation at investigational sites.

**Page 35, Section 6.2 Rationale for Study Design, Dosage, and Endpoints**

**Existing Text**

*(3)* Rationale for endpoints

•••

**Revised Text**

**(3) Rationale for dosage in Part A, Cohort 4**

19.**320 mg or 360 mg may be selected as the loading dose in the planned phase 3 multinational study. Based on this situation, a new cohort, Cohort 4, was added to Part A in Amendment 2 of the study protocol, designed to evaluate the tolerability of loading dose of 360 mg in Japanese patients before joining the phase 3 multinational study. As for the maintenance dose, the same dose as Part A, Cohort 2 (120 mg) was selected, since this dose is expected to keep serum testosterone at castration levels and maintain this effect.**

20. **As described in the section above, the tolerability of single doses of 360 mg and multiple doses as high as 160 mg (for 28 days) has been confirmed in a phase 1 study in healthy adult males that was conducted in Europe (TAK-385_C27001). [redacted] Based on the fact that there are no major differences between Japanese and Americans in the pharmacokinetic or pharmacodynamic profiles of TAK-385, and that there are no major differences between the pharmacokinetic profiles obtained in healthy adult men and women, there are no safety concerns in using the loading dose of 360 mg and maintenance dose of 120 mg in Part A, Cohort 4.**

**(4)** Rationale for endpoints

**•••**

**Rationale for Amendment**

Change based on the addition of Part A, Cohort 4.

**Page 47, Section 8.1.3 Dose and Regimen**

**Existing Text**

Table 8.a Cohorts, Dosages, and Numbers of Tablets (Part A)

| Cohort | Dosage/Number of Tablets |
|---|---|
| 1 | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 80 mg (Days 2 to 28): One 80 mg tablet per day |
| 2 | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 120 mg (Days 2 to 28): One 80 mg tablet and one 40 mg tablet per day |
| 3 | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 160 mg (Days 2 to 28): One 80 mg tablet and two 40 mg tablets per day |
| Additional cohort[*1] | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 40 mg (Days 2 to 28): One 40 mg tablet per day |

## Revised Text

Table 8.a Cohorts, Dosages, and Numbers of Tablets (Part A)

| Cohort | Dosage/Number of Tablets |
|---|---|
| 1 | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 80 mg (Days 2 to 28): One 80 mg tablet per day |
| 2 | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 120 mg (Days 2 to 28): One 80 mg tablet and one 40 mg tablet per day |
| 3 | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 160 mg (Days 2 to 28): One 80 mg tablet and two 40 mg tablets per day |
| **4** | **TAK-385 360 mg (Day 1): Three 80 mg tablets and three 40 mg tablet per day**<br>**TAK-385 120 mg (Days 2 to 28): One 80 mg tablet and one 40 mg tablet per day** |
| Additional cohort[*1] | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 40 mg (Days 2 to 28): One 40 mg tablet per day |

## Rationale for Amendment

Change based on the addition of Part A, Cohort 4.

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

## ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy HH:mm 'UTC') |
|---|---|---|
| [redacted] | Clinical Approval | 03-Oct-2017 10:10 UTC |

# CLINICAL STUDY PROTOCOL

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

Short Title: A Phase 1 Study of TAK-385 in Hormone Treatment-naive Patients With Prostate Cancer

| | | | |
|---|---|---|---|
| **Sponsor:** | Takeda Pharmaceutical Company Limited<br>1-1 Doshomachi 4-chome, Chuo-ku, Osaka | | |
| **Study Number:** | TB-AK160108 | | |
| **Version** | Amendment 1 | | |
| **IND Number:** | NA | **EudraCT Number:** | NA |
| **Study Drug:** | TAK-385 | | |
| **Date:** | 23 January 2015 | | |

# 1.0 STUDY ADMINISTRATION INFORMATION

## 1.1 Contacts and Responsibilities for Study-Related Activities

A separate contact information list will be provided to each site.

## 1.2 Principles of Clinical Studies

This study will be conducted with the highest respect for the individual participants in accordance with requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

## 1.3 Protocol Amendment Summary of Changes

The primary purpose of this amendment is to make changes to the protocol so that the study procedures match the situation at the investigational sites. Minor grammatical and editorial changes are also included. Full details on changes of text are given in Appendix J.

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## LIST OF APPENDICES

## 2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor:<br>Takeda Pharmaceutical Company Limited</td><td colspan="2">Study Drug:<br>TAK-385</td></tr>
<tr><td>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</td><td>IND Number:<br>NA</td><td>EudraCT Number:<br>NA</td></tr>
<tr><td>Study Number: TB-AK160108</td><td colspan="2">Phase: 1</td></tr>
<tr><td colspan="3">Study Design:<br>This study consists of two parts: Part A, a dose-rising phase, and Part B, an expansion phase.<br>In Part A, three to six patients will be enrolled in each cohort. Whether or not the study will proceed to the next cohort or Part B will be determined through assessment of tolerability at the dose in question, based on the incidence of dose-limiting toxicity (DLT) in the evaluation period. TAK-385 will be taken once a day for 28 days at the doses assigned to each cohort. Cohort 1 will receive a loading dose of 320 mg and a maintenance dose of 80 mg, Cohort 2 will receive a loading dose of 320 mg and a maintenance dose of 120 mg, and Cohort 3 will receive a loading dose of 320 mg and a maintenance dose of 160 mg. Patients being switched to a gonadotropin-releasing hormone (GnRH) agonist (eg, leuprorelin) or a GnRH antagonist (eg, degarelix) following the completion of TAK-385 treatment in Part A will first pass through a 1-week observation period (except for study withdrawals). Whether or not the study will proceed to Part B will be determined by the study sponsor after consulting the study monitoring committee (SMC) based on a comprehensive evaluation of the tolerability and safety data from Cohort 2 of Part A.<br>In Part B, subjects will be randomized to receive study drug (TAK-385 loading dose of 320 mg and maintenance dose of either 80 mg or 120 mg – equal numbers of subjects will be randomized to 80 mg and 120 mg) once a day orally to evaluate safety. In addition to the safety assessments, efficacy assessments will also be performed according to the study schedule, and study drug will be administered until the discontinuation criteria (Section 7.5) are met for each individual subject. After completing 48 weeks of treatment, subject may, at the discretion of the investigator, and depending on the wishes of the subject, continue receiving study drug (for a maximum of 96 weeks), or they may complete the study and be switched to a GnRH agonist or a GnHR antagonist, starting from the day after the day of the last dose of TAK-385.<br>All subjects who receive study drug will undergo safety follow-up 30 to 40 days after the last dose of TAK-385.</td></tr>
<tr><td colspan="3">Part A (Dose-rising phase)<br>Primary Objectives:<br>To evaluate the tolerability and safety of TAK-385 in hormone treatment-naive patients with non-metastatic prostate cancer.<br>Secondary Objectives:<br>To evaluate the pharmacokinetics (PK) and the effects on serum testosterone of TAK-385 in hormone treatment-naive patients with non-metastatic prostate cancer.<br>Part B (Expansion phase)<br>Primary Objectives:<br>To evaluate the safety of TAK-385 in hormone treatment-naive patients with non-metastatic prostate cancer.<br>Secondary Objectives:<br>To evaluate the change over time in the prostate-specific antigen (PSA) levels and the PK and effects on serum testosterone of TAK-385 in hormone treatment-naive patients with non-metastatic prostate cancer.</td></tr>
</table>

<table>
<tr><td colspan="2">Subject Population: Japanese patients with hormone treatment-naive non-metastatic prostate cancer</td></tr>
<tr><td>Numbers of Subjects<br>Part A: 3 to 6 subjects in each cohort (3 to 18 subjects in total)<br>Part B: 15 subjects in each group (30 subjects in total)</td><td>Number of Sites<br>Part A: 2 to 3 sites<br>Part B: Approximately 7 sites (some of the sites will be the same as the sites in Part A)</td></tr>
<tr><td>Dosage<br>Dosage: TAK-385 once a day orally at least 30 minutes before breakfast<br><u>Part A</u><br>Cohort 1: Loading dose of 320 mg and maintenance dose of 80 mg<br>Cohort 2: Loading dose of 320 mg and maintenance dose of 120 mg<br>Cohort 3: Loading dose of 320 mg and maintenance dose of 160 mg<br>(Additional cohort: Loading dose of 320 mg and maintenance dose of 40 mg)<br><u>Part B</u><br>80 mg group: Loading dose of 320 mg and maintenance dose of 80 mg<br>120 mg group: Loading dose of 320 mg and maintenance dose of 120 mg<br>(If there is an additional cohort in Part A, then instead of a 120 mg group, there will be a 40 mg group, which will received a loading dose of 320 mg and a maintenance dose of 40 mg.)</td><td>Route of Administration<br>Oral</td></tr>
<tr><td>Duration of Treatment<br>Part A: 28 days<br>Part B: 48 weeks (may be continued for up to a total of 96 weeks maximum)</td><td>Period of Evaluation<br>Part A: Approximately 2 months<br>Part B: Approximately 1 year (approx. 2 years if therapy is continued)</td></tr>
<tr><td colspan="2">Main Criteria for Inclusion<br>1. Patients with histologically or cytologically confirmed prostate cancer<br>2. Patients whose clinical diagnosis is T1-4 N0 M0, or Tx N0 M0 for patients who have undergone radical prostatectomy<br>3. Patients who have not received hormone therapy (eg, GnRH agonist, GnRH antagonist, steroidal antiandrogen, non-steroidal androgen) for prostate cancer<br>4. Patients with serum testosterone at screening > 150 ng/dL<br>5. Patients meeting either of the following criteria for PSA at screening<br>Untreated prostate cancer: PSA at screening > 4.0 ng/mL<br>Treated prostate cancer: PSA at screening > 0.2 ng/mL<br>6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1</td></tr>
</table>

**Main Criteria for Exclusion**

1. Patients exhibiting symptoms judged related to prostate cancer by the investigator (eg, bone pain, pelvic pain, ureteral obstruction) who urgently require hormone therapy such as GnRH agonist, GnRH antagonist, or combined androgen blockade (CAB)/maximum androgen blockade (MAB) therapy, chemotherapy, or radiotherapy
2. Patients who have received 5-alpha reductase inhibitors (except for patients who have been treated for male-pattern alopecias)
3. Treatment with any investigational compound within the 4 weeks (28 days) prior to the first dose of study drug or ongoing participation in another experimental trial related to the treatment of prostate cancer
4. Known hypersensitivity to TAK-385, TAK-385 excipients, or GnRH antagonists
5. Clinically relevant ECG abnormalities, or the following ECG abnormalities, at screening
   - Q-wave infarction, unless identified 6 or more months prior to TAK-385 treatment initiation
   - Fridericia corrected QT (QTcF) interval > 450 msec (when calculating the QTc interval, Fridericia's equation [$QT/RR^{0.33}$] will be used)
6. Patients with congenital QT prolongation

**Endpoints**

Part A

Primary endpoints

- DLTs, adverse events (AEs), clinical laboratory tests, vital signs, and 12-lead ECGs

Secondary endpoints

- Plasma concentrations of unchanged TAK-385
- Serum testosterone concentrations

Part B

Primary endpoints

- AEs, clinical laboratory tests, vital signs, and 12-lead ECGs

Secondary endpoints

- PSA levels
- Plasma concentrations of unchanged TAK-385
- Serum testosterone concentrations

**Statistical Consideations**

Safety analyses

1) Incidences of AEs

The following analysis will be performed for the safety analysis set.

Treatment-emergent adverse events (TEAEs) will be tabulated by part and dose. TEAEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT).

2) DLTs

The following analysis will be performed for the DLT analysis set.

The incidences of TEAEs judged to be DLTs in Part A will be tabulated by PT and dose.

3) Clinical laboratory test value profiles, vital signs, and 12-lead ECGs

The following analyses will be performed for the safety analysis set.

For continuous data, summary statistics will be calculated for the baseline values, the values observed at each assessment time point, and the changes from baseline by part and dose.

For categorical data and assessments based on reference values, cross tabulation of the values before and

after treatment (eg, normal/abnormal, qualitative clinical laboratory test values) will be performed by part and dose for each test parameter.

Pharmacokinetic analyses

Pharmacokinetic parameters (eg, maximum observed plasma concentration [Cmax], area under the plasma concentration - time curve [AUC]) will be evaluated using the plasma TAK-385 concentrations, and summary statistics will be calculated for the plasma concentrations and each of the pharmacokinetic parameters. Figures showing the changes over time in the plasma concentration of TAK-385 will also be prepared.

**Rationale for the Planned Sample Size**

Part A

Each cohort will have 3 or 6 subjects, based on the the guidelines on the clinical evaluation of antineoplastics

Part B

In order to detect less frequent AEs, 15 subjects per group (total of 30 subjects) were established as the number of cases enabling an approximately 80% chance of detecting AEs characterized by a true incidence of 10%.

## 3.0 LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| AMS | Aging Male's Symptoms |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the plasma concentration-time curve |
| BMI | body mass index |
| BMP | di-docosahexaenoyl (22:6)-bis(monoacylglycerol) phosphate |
| CAB | combined androgen blockade |
| CK-MB | creatine kinase MB |
| Cmax | maximum observed plasma concentration |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DHT | dihydrotestosterone |
| DLT | dose-limiting toxicity |
| eCRF | electronic case report form |
| ECOG | Eastern Cooperative Oncology Group |
| EORTC | European Organization for Research and Treatment of Cancer |
| EPIC | Expanded Prostate Cancer Index Composite |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GnRH | gonadotropin-releasing hormone |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| ICH | International Conference on Harmonisation |
| IEC | independent ethics committee |
| IRB | institutional review board |
| LFT | liver function test |
| LH | luteinizing hormone |
| MAB | maximum androgen blockade |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NOAEL | no-observed-adverse-effect level |
| PK | Pharmacokinetics |
| P-gp | P-glycoprotein |
| PGx | pharmacogenomics |
| PSA | prostate-specific antigen |
| PT-INR | Prothrombin Time-International Normalized Ratio |

| | |
|---|---|
| PTE | Pretreatment Event |
| QTc | corrected QT (interval) |
| QTcB | Bazett corrected QT |
| QTcF | Fridericia corrected QT |
| SHBG | sex hormone binding globulin |
| SMC | study monitoring committee |
| Tmax | maximum drug concentration time |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |

# 4.0 INTRODUCTION

## 4.1 Summary

In 2008 prostate cancer reached approximately 900,000 cases/year worldwide and is now the second leading cancer in men, accounting for 13.7% of cancer cases in men [1]. The median age of diagnosis is 70, and prostate cancer is rarely diagnosed in men under 40 [2]. Incidence increases with age and is expected to rise in the future as the population ages. In Japan, 2008 statistics show that prostate cancer ranks a high fourth in morbidity among cancers in men [3]. Prostate cancer in Japan also occurs more often with age, and the incidences increases rapidly in men 60 and older.

It is known that prostate cancer is to responsive to surgical castration and that the effectiveness of this therapy results from the elimination of androgen. This knowledge led to the understanding that most prostate cancers are growth hormone dependent and ever since this discovery, hormone therapy has played an important role in the treatment of prostate cancer.

Castration by orchiectomy or a gonadotropin-releasing hormone (GnRH) agonist is the main mode of therapy for localized progressive and metastatic cancers, and GnRH agonists such as leuprorelin acetate are widely used [4]. When multiple doses of a GnRH agonist are administered, a temporary increase in gonadotropin secretion (flare up) occurs. That is followed by a decrease in responsiveness (desensitization) in the pituitary gland and gonads, which appears to work effectively by inhibiting the secretion of sex hormones. The flare up sometimes leads to a temporary worsening of symptoms, and the effectiveness of GnRH agonist begins to appear about 3 to 4 weeks after the initial dose. In addition, the GnRH is a peptide formulation and is unable to be administered orally. Consequently, development of a new medication that is easy to administer and does not cause flare ups is needed.

TAK-385 is a non-peptide orally active GnRH antagonist with a novel structure that was discovered by Takeda Pharmaceutical Company, Ltd. TAK-385 antagonizes GnRH at the GnRH receptors present in the basophils (secreting cells) of the anterior pituitary gland and inhibits the GnRH-stimulated secretion of gonadotropin luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from those cells. This action lowers the serum testosterone concentration in the blood. An antitumor effect is expected in prostate cancer patients due to the suppression of serum testosterone production by the testes. TAK-385 is also expected to manifest its effects rapidly without causing flare ups like GnRH agonists. Moreover, because it is a non-peptide formulation, TAK-385 can be administered orally, unlike peptide-based GnRH agonists that must be absorbed subcutaneously. The clinical pharmacokinetic and pharmacodynamic profiles may offer additional advantages compared with a depot peptide formulations, such as more rapid recovery from short term medical castration.

Takeda Pharmaceutical Co., Ltd. decided to develop TAK-385 for the treatment of prostate cancer both overseas and in Japan. Moreover, development of TAK-385 in Japan and Asia for endometriosis and uterine fibroids is already underway.

### 4.1.1 Nonclinical Summary

#### 4.1.1.1 Pharmacology Related to the Proposed Mechanism of Action

A series of in vitro and in vivo pharmacological studies have demonstrated that TAK-385 acts as a potent and highly selective antagonist for human GnRHR (hGnRHR).

[redacted] [5].

#### 4.1.1.2 Safety Pharmacology

In safety pharmacology studies, [redacted]

[redacted] [5].

#### 4.1.1.3 Pharmacokinetics and Product Metabolism in Animals

[redacted]

[5].

#### 4.1.1.4 Toxicology

TAK-385 has been evaluated for safety in single- and repeat-dose toxicity studies, with supportive toxicokinetic analyses, in mice, rats, and monkeys. Genetic, carcinogenicity, reproductive, and phototoxicity studies have also been performed.

[redacted]

[redacted] [5].

[redacted]

### 4.1.2 Clinical Studies

4.1.2.1 Japanese Phase 1 Single- and Multiple-dose Study ([redacted])

A placebo-controlled double-blind single dose study of the safety, pharmacokinetics (PK), and pharmacodynamics of TAK-385 was conducted in 72 premenopausal healthy adult Japanese women (including 12 in the placebo group). Moreover, a crossover study comparing fasted state/postprandial administration, and fasted/preprandial administration was conducted in 24 premenopausal healthy women to investigate the effect of meals on TAK-385 PK. In addition, a placebo-controlled double-blind, 14-day multiple dose study of safety, PK, and pharmacodynamics during of TAK-385 was conducted in 48 premenopausal healthy adult women (including 12 in the placebo group).

[redacted]

[redacted]

[5].

4.1.2.2 Overseas Phase 1 Single- and Multiple-dose Study ([redacted])

A placebo-controlled double-blind single-dose study of the safety, PK, and pharmacodynamics of TAK-385 was conducted in 72 premenopausal healthy adult American women (including 12 in the placebo group). Moreover, a crossover study comparing fasted with fed (post-breakfast) administration was conducted in 12 premenopausal healthy women to investigate the effect of food on the PK of TAK-385. In addition, a placebo-controlled double-blind, 14-day multiple dose study of safety, PK, and pharmacodynamics during of TAK-385 was conducted in 36 premenopausal healthyadult women (including 9 in the placebo group).

[redacted] [5].

4.1.2.3 Japanese Phase 1 Study of Drug-drug Interactions With Erythromycin ([redacted])

A phase 1 open-label drug-drug interaction study was carried out in healthy Japanese male and female subjects to evaluate the effect of multiple doses (300 mg, q.i.d.) of erythromycin (moderate CYP3A4 inhibitor and P-gp inhibitor) on the single-dose PK of TAK-385 (20 mg). [redacted] [5].

4.1.2.4 Overseas Phase 1 Drug-drug Interaction Study ([redacted])

[redacted]

[redacted] [5].

4.1.2.5 Overseas Phase 1 Single- and Multiple-dose Study (TAK-385_C27001)

Study C27001 was a phase 1 study that evaluated the safety, tolerability, PK, and PD of TAK-385 in 176 healthy English adult male subjects (128 subjects received TAK-385) receiving single doses of TAK-385 up to 360 mg QD and multiple doses of TAK-385 up to 180 mg QD for up to 28 days. The study had 4 parts: Part 1 included single-dose administration of TAK-385 to 32 subjects across 4 dose cohorts plus placebo and had a fed/fasted arm; Part 2 included multiple dose administration of TAK-385 for 14 days to 40 subjects across 5 dose cohorts plus placebo; and Parts 3 and 4 included multiple dose administration of TAK-385 for 28 days to 66 and 38 subjects, respectively, across 2 dose cohorts (a total of 4 dose levels), plus placebo.

There were no deaths or SAEs following single-dose or multiple-dose treatment with TAK-385 for 14 or 28 days.

Following 28 days of QD dosing, there were 3 discontinuations due to drug-related, hepatic AEs: 2 subjects in the 160 mg dose cohort in Part 3 of the study discontinued treatment due to Grade 1 AEs of hepatic enzyme increased (ALT and AST); and 1 subject in the 60 mg dose cohort in Part 4 of the study discontinued treatment due to a Grade 2 AE of liver function test (LFT) abnormal (ALT and AST). There was no clear trend between dose level and toxicity, although abnormal liver transaminase levels appeared more likely to occur within 2 weeks at higher dose levels. All AEs resolved by the end of the study.

The majority of subjects had at least 1 AE, but no increase in the incidence of AEs with increasing dose of TAK-385 was observed. The most common AEs observed across all dose cohorts were bradycardia, hot flush, and headache, and the most common, drug-related AE was hot flush.

A number of cardiac AEs according to Common Terminology Criteria for Adverse Events (CTCAE) were reported, but for these subjects the ECG interpretation was considered to be not clinically significant by the investigator. These cardiac AEs included electrocardiogram QT prolonged (1 AE in Part 1, 4 AEs in Part 2, and 7 AEs in Part 3) and first degree atrioventricular block (2 AEs in Part 1 and 6 AEs in Part 2). Changes in mean QTc interval of approximately 15 to 20 msec were noted before administration on Day 14 (80 to 180 mg QD) in adult male subjects in this study. The QTc changes were independent of drug administration, not correlated to drug levels, and are similar to those observed in surgical and medical castration studies with other compounds. No major

safety concerns were noted in healthy male subjects receiving single (80 to 360 mg) and multiple (20 to 180 mg) doses of TAK-385, and TAK-385 was well tolerated.

Single doses of 80 to 360 mg of TAK-385 administered orally (fasted state) were absorbed rapidly in plasma with median Tmax values ranging from 1.75 to 4.00 hours after administration across the entire dose range. After attaining Cmax, TAK-385 plasma concentrations declined in a multi-exponential manner with a mean T1/2 ranging from 19.1 to 21.7 hours. The mean Cmax and AUC values for TAK-385 generally increased in an approximately dose-proportional manner over the 80 to 360 mg dose range.

When a multiple dose of 20 to 180 mg QD of TAK-385 was administered, the drug was readily absorbed in plasma on Days 1 and 14, and Cmax typically occurred within 1 to 2 hours after dosing. After attaining Cmax, individual PK profiles on Day 14 exhibited a multi-exponential elimination phase with a mean elimination phase T1/2 of approximately 36 to 65 hours at doses of 20 to 180 mg QD. The trough concentration-time data (Day 2, and Days 11 to 14) implied that steady-state conditions were attained within approximately 10 days.

Similarly, the effect of food was studied in 6 male subjects in the crossover period (Part 1). Compared to fasting conditions, the absorption of TAK-385 in plasma decreased and was delayed following a single 180 mg dose taken 30 minutes after the start of a standard FDA high-fat, high-calorie breakfast. Least square mean Cmax and AUC(0-inf) values decreased by approximately 52% and 47%, respectively. Furthermore, median Tmax increased from 1.75 hours to 5.00 hours under fed conditions. When the dose was administered 30 minutes prior to the standardized morning meal (Part 2), systemic exposure to TAK-385 appeared to be reduced to a lesser extent (approximately 28% on average) and no changes in the absorption rate were observed.

In this study, serum LH, FSH, dihydrotestosterone (DHT), and testosterone concentrations were determined following single and multiple oral doses of TAK-385 or placebo for up to 28 days. TAK-385 caused an immediate and effective suppression of gonadotropins (LH, FSH) and testosterone. While no changes were observed in the placebo group, serum testosterone levels were markedly suppressed in all TAK-385 dose groups within the first 3 days of administration. Loading doses of 320/240/160 mg for up to 3 days and doses of 180 mg or greater led to testosterone levels below the conventional castration level within 48 hours. The onset of the testosterone lowering response shortened as the loading dose increased. This phenemon was likely a result of higher TAK-385concentrations in the blood. Similar dose-dependent suppressive effects were observed after a single oral dose. These findings support the principal mechanism of action that, as a GnRH antagonist, TAK-385 competitively binds with the pituitary GnRH receptors.

In administration over 28 days in Part 3 and 4, both 160 mg and 80 mg QD were effective at achieving conventional medical castration levels during the third and fourth weeks of multiple administration. Despite the loading dose regimen, however, the 40-mg QD dose was ineffective in maintaining castration levels between Days 14 and 28. The results at 60 mg QD were intermediate to those of 40 and 80 mg QD and suggested that the likely

minimal, fully effective maintenance dose for medical castration would be 80 mg QD or above [5].

## 4.2 Rationale for the Proposed Study

The results of the phase 1 study conducted in England (TAK-385_C27001) demonstrate the tolerability of multiple doses of TAK-385 (20 to 80 mg) in healthy adult men. Moreover, the plasma concentration of TAK-385 increased as the dose increased, and rose slightly greater than dose proportionality. The blood concentrations of the measured hormones all decreased rapidly with multiple doses of TAK-385 and effective suppression of serum testosterone was sustained throughout the adminsitration period.

Because prostate cancer is a sex-hormone dependent disease, and an antitumor effect is expected as a result of lowering hormone concentrations in the blood through administration of TAK-385, it was decided to conduct a phase 1 study in patients with prostate cancer.

This protocol was prepared in accordance with the Good Clinical Practice (GCP).

# 5.0 STUDY OBJECTIVES AND ENDPOINTS

## 5.1 Objectives

### 5.1.1 Primary Objectives

Part A

To evaluate the tolerability and safety of TAK-385 in hormone treatment-naive patients with non-metastatic prostate cancer.

Part B

To evaluate the safety of TAK-385 in hormone treatment-naive patients with non-metastatic prostate cancer.

### 5.1.2 Secondary Objectives

Part A

To evaluate the PK and the effects on serum testosterone of TAK-385 in hormone treatment-naive patients with non-metastatic prostate cancer.

Part B

To evaluate the change over time in the prostate-specific antigen (PSA) levels and the PK and effects on serum testosterone of TAK-385 in hormone treatment-naive patients with non-metastatic prostate cancer.

## 5.2 Endpoints

### 5.2.1 Primary Endpoints

Part A

Safety: Dose-limiting toxicities (DLTs), AEs, clinical laboratory tests, vital signs, and 12-lead ECGs

Part B

Safety: AEs, clinical laboratory tests, vital signs, and 12-lead ECGs

### 5.2.2 Secondary Endpoints

Part A

PK: Plasma concentrations of unchanged TAK-385

Pharmacodynamics: Serum testosterone concentrations

Part B

Efficacy: PSA levels

PK: Plasma concentrations of unchanged TAK-385

Pharmacodynamics: Serum testosterone concentrations

### 5.2.3 Additional Endpoints

Part A

Efficacy: PSA levels

Pharmacodynamics: LH, FSH, DHT, and sex hormone binding globulin (SHBG) serum concentrations

Part B

Safety: Bone density [6]

Efficacy: Disease progression assessed by PSA, disease progression assessed by imaging

Pharmacodynamics: LH, FSH, DHT, and SHBG serum concentrations

Other: QOL assessments based on the Aging Male's Symptoms (AMS) [7], European Organization for Research and Treatment of Cancer (EORTC)-QLQ-C30 [8, 9, 10], and the Expanded Prostate Cancer Index Composite (EPIC) [11, 12]

# 6.0 STUDY DESIGN AND DESCRIPTION

## 6.1 Study Design

This is a multicenter phase 1, open-label, dose range-finding study to evaluate the tolerability, safety, PK, and pharmacodynamics of TAK-385 alone in hormone treatment-naive Japanese patients with non-metastatic prostate cancer.

This study consists of two parts: Part A, a dose-rising phase, and Part B, an expansion phase. The designs of Part A and Part B are shown in "Study Design and Treatment Schema" (Figure 6.a and Figure 6.b).

In Part A, three to six patients will be enrolled in each cohort. Whether or not the study will proceed to the next cohort or Part B will be determined through assessment of tolerability at the dose in question, based on the incidence of DLT in the evaluation period (treatment initiation to Day 28).

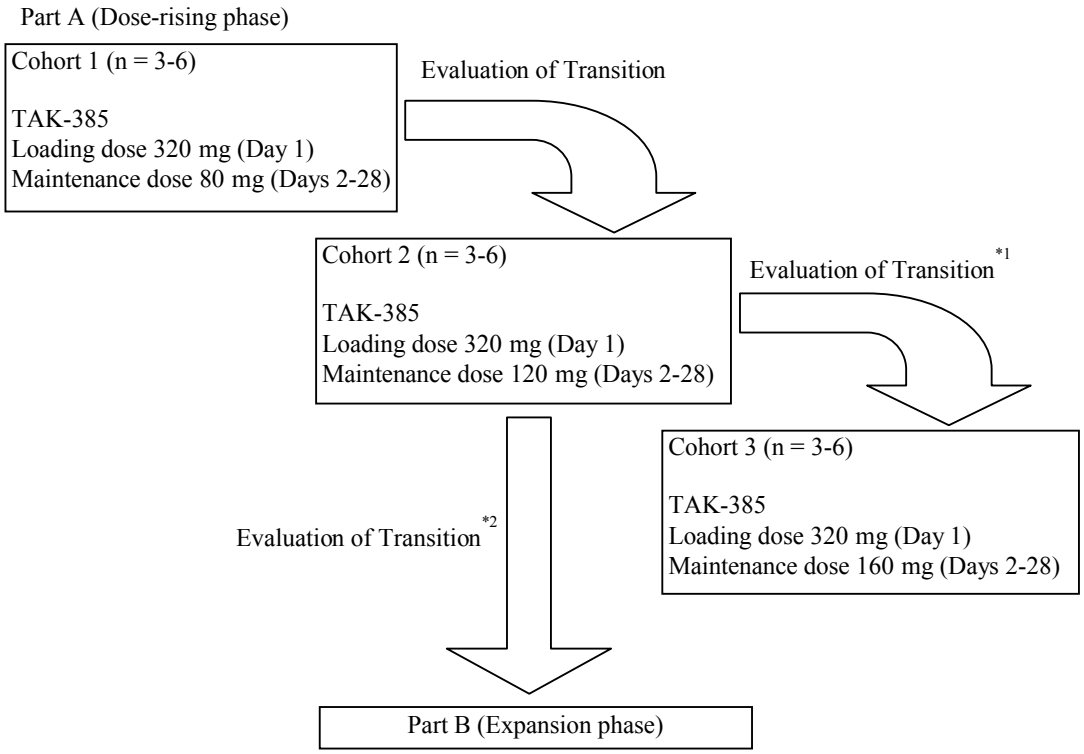
TAK-385 will be taken once a day for 28 days at the doses assigned to each cohort. Cohort 1 will receive a loading dose of 320 mg and a maintenance dose of 80 mg, Cohort 2 will receive a loading dose of 320 mg and a maintenance dose of 120 mg, and Cohort 3 will receive a loading dose of 320 mg and a maintenance dose of 160 mg. The doses will be taken orally at least 30 minutes before breakfast. Patients being switched to a GnRH agonist (eg, leuprorelin) or a GnRH antagonist (eg, degarelix) following the completion of TAK-385 treatment in Part A will first pass through a 1-week observation (no-treatment) period. However, patients whose treatments were discontinued because they met the discontinuation criteria (Section 7.5) during the 28-day treatment period will not have to pass through this observation period.

If tolerability is confirmed in Cohort 2, then the study will proceed to Cohort 3 and Part B simultaneously. The tolerability in Japanese of the maximum dose at which tolerability was found in 28-day multiple dosing in the overseas phase 1 single-/multiple-dose study (TAK-385_C27001) (160 mg) will be evaluated for the purpose of checking the tolerability of dose escalation to 160 mg in Part B as well as the PK. In the overseas phase 1 single-/multiple-dose study (TAK-385_C27001), no findings indicative of safety problems were obtained in multiple dosing for 28 days with 160 mg. However, if tolerability is not confirmed in Cohort 2, then a cohort will be added that will receive a loading dose of TAK-385 320 mg and a maintenance dose of 40 mg.

In Part B, subjects will be randomized to receive study drug (TAK-385 loading dose of 320 mg and maintenance dose of either 80 mg or 120 mg – equal numbers of subjects will be randomized to 80 mg and 120 mg) once a day orally to evaluate safety. In addition to the safety assessments, efficacy assessments will also be performed according to the study schedule, and study drug will be administered until the discontinuation criteria (Section 7.5) are met for each individual subject. After completing 48 weeks of treatment, subjects may, at the discretion of the investigator, and depending on the wished of the subhect, continue receiving study drug (for a maximum of 96 weeks), or they may complete the study and be switched to a GnRH agonist (eg, leuprorelin) or a GnHR antagonist (eg, degarelix), starting from the day after the day of the last dose of TAK-385. Subjects withdrawing from the study will not be replaced.

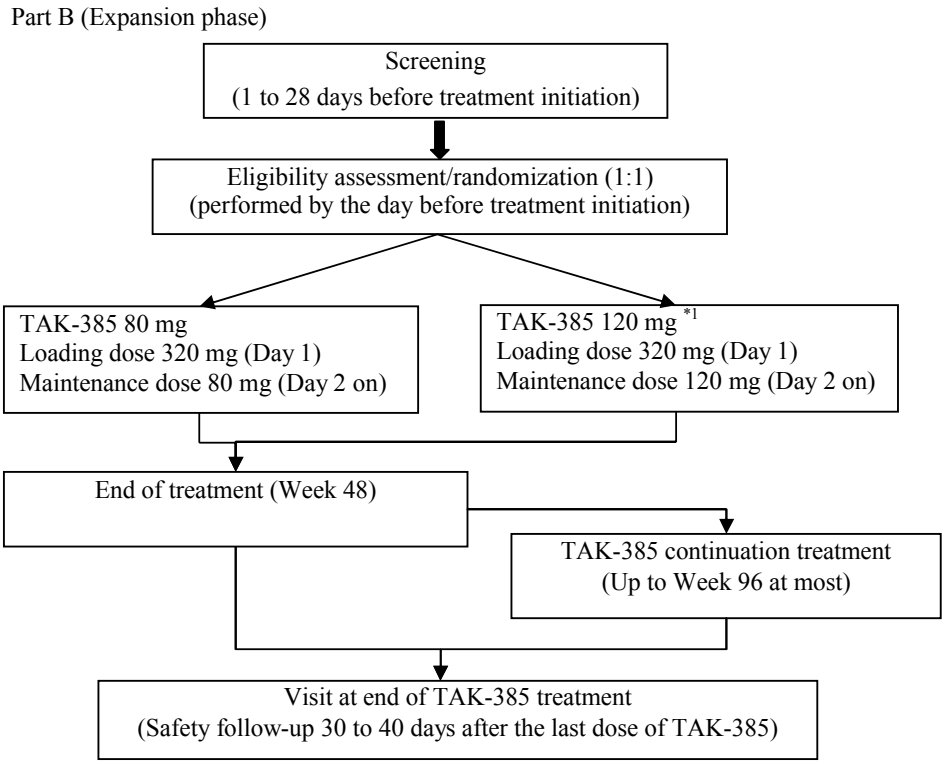
If no problems with tolerability are found in the additional cohort in Part A, then the study will proceed to Part B with a 40 mg group instead of a 120 mg group (TAK-385 loading dose of 320 mg and maintenance dose of 40 mg).

All subjects who receive study drug, whether in Part A or Part B, will undergo safety follow-up 30 to 40 days after the last dose of TAK-385.




*1: If tolerability is not confirmed in Cohort 2, then a cohort will be added which will receive a loading dose of 320 mg and a maintenance dose of 40 mg.
*2: If a cohort is added, and the additional cohort continues to the end and no problems with tolerability are found, then the study will proceed to Part B.

**Figure 6.a. Study Design and Treatment Schema (Part A)**




*1: If a cohort is added in Part A, then in Part B 120 mg group will be replaced to 40 mg group, in which subjects will receive loading dose of 320 mg and maintenance dose of 40 mg.

**Figure 6.b Study Design and Treatment Schema (Part B)**

Figure 6.a and Figure 6.b show an overview of the study schedule. See Appendix A through Appendix D for a more detailed schedule of the study tests, observations, and assessments.

**Table 6.a Study Schedule (Part A)**

| Screening | | Treatment Period<br>DLT Evaluation Period (treatment initiation to Day 28) | | Post-treatment Observation Period | | Safety Follow-up |
|---|---|---|---|---|---|---|
| Outpatient | | Inpatient | Outpatient | Outpatient/Inpatient | | Outpatient |
| Day -28 to Day -1*1 | | Day 1*1 to Day 15 | Day 16 to Day 28*2 | Day 29 to Day 35*2 | ... | 30 to 40 days after the last dose of TAK-385 |
| Screening tests<br>Assessment of eligibility | Admission | Tests/observations<br>Treatment initiation<br>Discharge | Treatment completion<br>Tests/observations | Tests/observations<br>Initiation of other treatment | Observations | Tests/observations |

*1: Day -1 and Day 1 are the day before treatment initiation and the day of treatment initiation, respectively.
*2: Days 27 to 35 are performed either on an outpatient or an inpatient basis.

**Table 6.b Study Schedule (Part B)**

| Screening | Treatment Period | Continuation Treatment Period | Safety Follow-up |
|---|---|---|---|
| Outpatient | | | |
| Days -28 to -1[*1] | Week 1, Day 1[*1] to Week 48, Day 7[*2] | Week 49, Day 1 to Week 96, Day 7[*2] | 30 to 40 days after the last dose of TAK-385 |
| Screening tests<br>Assessment of eligibility, randomization | Tests, observations<br>Treatment initiation<br>Treatment completion | Tests, observations<br>Treatment initiation<br>Treatment completion | Initiation of other treatment<br>Tests, observations |

*1: Day -1 and Day 1 are the day before treatment initiation and the day of treatment initiation, respectively.
*2: Other treatments may be initiated starting on the day after the day of the last dose of TAK-385 (Week 48, Day 8 or Week 96, Day 8).

### 6.1.1 Cohort/Part Advancement Criteria

Whether or not the study will proceed to the next cohort in Part A will be determined by the study sponsor after consulting the study monitoring committee (SMC) and following a comprehensive evaluation of the safety data based on the number of subjects experiencing DLT in each cohort (Table 6.c). Drug will be administered to the subjects in the next cohort after the decision on cohort advancement is made. See the separately prepared written procedures for detailed study advancement criteria.

In each cohort, if no DLT occurs in even 1 of the 3 subjects during the DLT evaluation period (see Section 6.1.2.2), then the dose will be judged tolerable, and the study will proceed to the next cohort. If a DLT occurs in 1 subject in the DLT evaluation period, and additional 3 subjects will be enrolled in this cohort, and DLT will be evaluated in a total of 6 subjects. If DLT occurs in 1 of these 6 subjects, this dose will be judged tolerable, and the study will proceed to the next cohort. If DLT occurs in 2 or more subjects, the study will be stopped, but if it is determined, after consulting the SMC, that this dose is tolerable, then the study will proceed to the next cohort.

Whether or not the study will proceed to Cohort 3 and Part B will be determined by the study sponsor after consulting the SMC based on a comprehensive evaluation of the tolerability and safety data from Cohort 2 of Part A.

If the study cannot proceed from Cohort 2 to Cohort 3 and Part B because of a tolerability problem, the study will proceed to an additional cohort that will receive a TAK-385 loading dose of 320 mg and a maintenance dose of 40 mg. In this case, as well, 3 subjects will be enrolled, and assessed in the same manner as described above. If the study proceeds to the additional cohort, and continues until the treatment of the additional cohort has been completed, and it is confirmed that no problems with tolerability are found, then the study will proceed to Part B.

If DLT occurs in 2 or more subjects in Cohort 3, then whether or not to increase the dose to 160 mg in Part B will be determined in consultation with the SMC.

Because assessment of the MTD is not the objective of this study, additional subjects will not be enrolled if TAK-385 is found to be tolerable in an evaluation of the 3 subjects in Cohort 3, nor will additional subjects be enrolled at lower dose levels if TAK-385 is not found to be tolerable at the dose level initially investigated.

**Table 6.c Cohort/Part Advancement Criteria**

| Number of Subjects With DLT (DLT evaluable subjects) | Cohort | Procedure |
|---|---|---|
| 0/3 | 1 | Proceed to Cohort 2 |
| | 2 | Proceed to Cohort 3 and Part B |
| | 3 | Stop |
| 1/3 | 1 to 3 | Add 3 subjects in the same cohort |
| 2/3 or 3/3 | 1 | Stop |
| | 2 | Add a cohort*1 |
| | 3 | Stop |
| 1/6 | 1 | Proceed to Cohort 2 |
| | 2 | Proceed to Cohort 3 and Part B |
| | 3 | Stop |
| ≥ 2/6 | 1 | Stop |
| | 2 | Add a cohort*1 |
| | 3 | Stop |

*1: TAK-385 loading dose of 320 mg and maintenance dose of 40 mg

**Table 6.d Criteria for Advancing From an Additional Cohort to Part B**

| Number of Subjects With DLT (DLT evaluable subjects) | Procedure |
|---|---|
| 0/3 | Proceed to Part B |
| 1/3 | Add 3 subjects |
| 2/3 or 3/3 | Stop |
| 1/6 | Proceed to Part B |
| ≥ 2/6 | Stop |

### 6.1.2 DLT

#### 6.1.2.1 Definition of DLT

DLTs are defined at treatment-related AEs that occur within the first 28 days of treatment and that meet one of the criteria described below based on CTCAE Version 4.03 (issued June 14, 2010) [13].

1. Grade 3 or higher toxicity

   Clinical laboratory abnormalities meet this criterion if they are found at 2 consecutive time points 7 or more days apart, except for ALT or AST > 3 × upper limit of normal(ULN), total bilirubin > 2 × ULN, or prothrombin time-international normalized ratio (PT-INR) > 1.5 at 2 time points 2 or more days apart.

2. Either of the following ECG findings at 2 time points 7 or more days apart

   - QT/Fridericia corrected QT (QTcF) > 500 msec after treatment initiation
   - QT/QTcF interval prolongation > 60 msec postdose

   The QTcF interval will be calculated using Fridericia's equation ($QT/RR^{0.33}$).

If it is difficult to determine whether or not an event is a DLT and the subject who experienced the event should be included in the DLT analysis set, the sponsor will consult the SMC before making a final decision on whether or not the event is a DLT.

Study treatment will be continued until the end of the 28-day treatment period unless a DLT occurs. If a subject is withdrawn from the study for a reason other than a DLT or if treatment compliance is below 80% (23 doses), the subject will be considered ineligible for inclusion in the DLT analysis set, and replacement subjects will be added in order to obtain 3 or 6 evaluable subjects.

#### 6.1.2.2 DLT Evaluation Period

From treatment initiation until Day 28 in Part A.

#### 6.1.2.3 DLT Evaluable Subjects

Subjects meeting any of the following criteria enrolled in a cohort in Part A.

- Subjects who have taken at least 80% of the doses of TAK-385 (23 doses) during the DLT evaluation period and for whom the DLT evaluation period observations have been completed.
- Subjects who experienced DLTs during the DLT evaluation period.

## 6.2 Rationale for Study Design, Dosage, and Endpoints

(1) Rationale for the target patient population and the study design

The novel GnRH antagonist TAK-385 is expected to compensate for the deficiencies of the GnRH agonists that have been widely used in the treatment of prostate cancer to date, and is being developed as a novel therapeutic medication for prostate cancer. The target patient population for this study was therefore made Japanese patients with prostate cancer.

Because this study will be the first time in Japan that TAK-385 will be administered to patients with prostate cancer, and the safety and efficacy of TAK-385 for the target population have not been sufficiently demonstrated, the TAK-385 treatment period in Part A was set at 28 days. The treatment period would minimize the inconvenience

to subjects with safety concerns or insufficient efficacy. Because TAK-385 will be administered alone to hormone treatment-naive patients with prostate cancer, a placebo would not be used, and that the study would be conducted as an open-label study. It was also decided that if a subject is going to be switched to some other therapy after receiving the last dose of TAK-385 in Part A, then the patient would have to first pass through a 1-week observation (no-treatment) period because of concerns about the safety of the temporary concomitant use of TAK-385 with other therapies. However, subjects meeting the discontinuation criteria (Section 7.5) during the 28-day treatment period would not need to first pass through a 1-week observation period if they need to be switched to some other therapy immediately.

The treatment period in Part B was made 48 weeks long in order to investigate safety and efficacy over a longer period, in light of the fact that the safety and efficacy of TAK-385 in multiple dosing for 28 days will have been confirmed in Part A. If the investigator determines after 48 weeks that there are no safety problems and that TAK-385 treatment may be continued, then treatment may be continued for up to a total of 96 weeks. Part B was made an open-label phase with randomization to one of two doses the tolerability of which will have been confirmed in Part A. An open-label study design was used because TAK-385 is being administered alone to hormone treatment-naive patient with prostate cancer. In addition, if a subject is going to be switched to some other treatment after the last dose of TAK-385 then, unlike in Part A, and assuming use in the actual clinical setting, it was decided that the other therapy could be initiated without any intervening observation period for confirming the safety of temporary concomitant use with the other therapy.

Furthermore, TAK-385 has been found to be affected by food, and the results that have been obtained suggest that TAK-385 absorption is decreased and delayed when a single dose is taken 30 minutes after food compared to when it is taken in a fasted condition (TAK-385_C27001). It was therefore decided that TAK-385 should be taken at least 30 minutes before breakfast.

Because the company plans to participate in multinational studies in the future, it was decided that Part B would be conducted using the same dosage and administration as that being used in the phase 2 studies being conducted overseas. Because Part B will be conducted using a dosage the tolerability of which will have been confirmed in Cohorts 1 and 2 in Part A, it was decided that Part A Cohort 3 and Part B could be conducted in parallel.

(2) Rationale for loading dose (Part A, Cohort 1)

In a phase 1 study in healthy adult males that was conducted in Europe (TAK-385_C27001), the tolerability of single doses as high as 360 mg and multiple doses as high as 160 mg was confirmed. In order to keep serum testosterone at castration levels and maintain this effect, it was felt that a dose of at least TAK-385 80 mg a day would be necessary as a maintenance dose. In addition, in study TAK-385_C27001, single doses of TAK-385 180 mg and above reduced serum testosterone levels to castration levels within 48 hours.

Based on these existing data on TAK-385 and on the development plan, it was decided that the loading dose for Cohort 1 in Part A of this study should be 320 mg, a dose that is within the range of doses that have been confirmed to be safe in single dosing, and that can be reliably expected to suppress serum testosterone levels within 48 hours. Given that TAK-385 is going to be used in patients with prostate cancer, the company concluded that it would be necessary to use a dose that could be expected to be effective from the beginning, and that this dose would be tolerated as the loading dose in Japanese. The maintenance dose was set at 80 mg, which can be expected to suppress serum testosterone levels.

(3) Rationale for endpoints

1) Rationale for the primary endpoints

The endpoint in Part A is DLT, in order to confirm the tolerability of TAK-385 in multiple dosing. AEs, clinical laboratory tests, vital signs, and 12-lead ECGs were also made primary endpoints, in order to confirm safety.

In part B, the primary endpoints were made AEs, clinical laboratory tests, vital signs, and 12-lead ECGs, in order to confirm the safety of the use of TAK-385 in multiple dosing for 48 weeks.

2) Rationale for secondary endpoints

In both Part A and Part B, the plasma concentrations of unchanged TAK-385 will be investigated in order to confirm the PK of TAK-385 in multiple dosing. The change in serum testosterone levels over time will also be investigated, in order to confirm the pharmacodynamics. In addition, in Part B, PSA levels will also be evaluated in order to investigate the efficacy of TAK-385 in prostate cancer.

3) Rationale for other endpoints

In Part A, the changes over time in the blood levels of LH, FSH, DHT, and SHBG, which are involved in testosterone synthesis, will be investigated. PSA levels will also be evaluated, in order to preliminarily investigate the efficacy of TAK-385 in prostate cancer.

In Part B, disease progression assessed on the basis of PSA and disease progression assessed on the basis of imaging assessments will be evaluated in accordance with the Prostate Cancer Handling Guidelines, Fourth Edition [16], in order to preliminarily investigate the efficacy of TAK-385 in prostate cancer. In

addition, as in Part A, the changes over time in the blood levels of LH, FSH, DHT, and SHBG will also be investigated. Moreover, because androgen-deprivation therapy is known to promote loss of bone mineral density and increase the potential for bone fractures, bone density tests were specified in order to evaluate the effects of TAK-385 on bone mineral density. In nonclinical studies, changes suggesting systemic phospholipidosis have been found in the organs/tissues of animals. Therefore, in order to closely monitor subjects for phospholipidosis, ophthalmology tests were specified, as was assessment of the level of di-docosahexaenoyl (22:6)-bis(monoacylglycero)phosphate (BMP) [14, 15]. Furthermore, in order to evaluate the effects of TAK-385 on quality of life in patients with prostate cancer, quality of life assessments will be performed using the Japanese versions of AMS, EORTC-QLQ-C30, and EPIC, which are widely used in clinical studies overseas.

## 6.3 Premature Termination or Suspension of Study or Investigational Site

### 6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the product, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- The SMC recommends that the study be suspended or terminated.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

### 6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

An investigational site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

### 6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

## 7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All inclusion and exclusion criterial, including test results, need to be checked before study treatment initiation (Part A) or randomization (Part B).

### 7.1 Inclusion Criteria

Subject eligibility will be determined based on the following criteria.

1. Patients judged by the investigator to have the capacity to understand the study and follow the study rules.
2. Patients whose written consent (signature or printed name and personal seal on informed consent form) can be obtained before any study procedures are performed.
3. Japanese male patients 20 or more years of age at the time of informed consent.
4. Patients who, if they have a female partner who could become pregnant, agree to practice appropriate means of contraception from the time of informed consent throughout the entire study treatment period and for 4 months after the last dose of study drug.
5. Patients in stable medical condition, including the absence of acute exacerbations of chronic illnesses, serious infections, or major surgery within 4 weeks (28 days) prior to study treatment initiation.
6. Patients with histologically or cytologically confirmed prostate cancer.
7. Patients whose clinical diagnosis is T1-4 N0 M0, or Tx N0 M0 for patients who have undergone radical prostatectomy.
8. Patients who are considered eligible for hormone therapy for prostate cancer.
9. Patients who have not received hormone therapy (eg, GnRH agonist, GnRH antagonist, steroidal antiandrogen, non-steroidal androgen) for prostate cancer.
10. Patients who have not undergone surgical castration.
11. Patients with serum testosterone at screening > 150 ng/dL.
12. Patients meeting either of the following criteria for PSA at screening.
    - Untreated prostate cancer: PSA at screening > 4.0 ng/mL
    - Treated* prostate cancer: PSA at screening > 0.2 ng/mL

*: Patients who have undergone prostatectomy or either or both of high intensity focused ultrasound therapy or radiotherapy (excluding $^{125}$I-brachytherapy) prior to the start of this study.

13. Eastern Cooperative Oncology Group (ECOG) performance status [17] of 0 or 1 (Appendix G)
14. Body mass index (BMI*) at screening ≥ 18.0 kg/m$^2$

*: BMI will be calculated by the investigational site using the following formula: BMI = Body weight (kg)/(height (m))$^2$

Body weight will be measured in kilograms to the first decimal point, height will be measured in centimeters using integers only, and the results obtained for BMI will be rounded off to the first decimal point.
Example: Weight = 79.2 (kg), height = 176 (cm) = 1.76 (m); BMI = $79.2/1.76^2 = 25.6$ ($kg/m^2$)

## 7.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study.

1. Patients exhibiting symptoms judged related to prostate cancer by the investigator (eg, bone pain, pelvic pain, ureteral obstruction) who urgently require hormone therapy such as GnRH agonist, GnRH antagonist, or combined androgen blockade (CAB)/ maximum androgen blockade (MAB) therapy, chemotherapy, or radiotherapy.
2. Patients who have received 5-alpha reductase inhibitors (except for patients who have been treated for male-pattern alopecias).
3. Patients who have received chemotherapy for prostate cancer (including estramustine).
4. Patients who have received $^{125}$I-brachytherapy.
5. Patients who received radiotherapy (except for $^{125}$I-brachytherapy) within 16 weeks (112 days) before study treatment initiation.
6. Patients who underwent prostatectomy within 16 weeks (112 days before study treatment initiation.
7. Treatment with any investigational compound within the 4 weeks (28 days) prior to the first dose of study drug or ongoing participation in another experimental trial related to the treatment of prostate cancer.
8. Diagnosis or treatment for another systemic malignancy within 2 years before study treatment initiation, or who had received a diagnosis of another malignancy before that and have evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ who have undergone complete resection will not be excluded from the study.
9. Patients taking drugs with moderate to strong CYP3A4 inhibitory or inducing effects, or any medications, supplements, or food products with P-gp inhibitory effects, in the 2 weeks (14 days) prior to study treatment initiation.
10. Patients who have received TAK-385 in a past clinical study.
11. Patients for whom it would be difficult to collect blood from a peripheral vein.
12. Patients with uncontrolled and clinically significant nervous, circulatory, pulmonary, hepatic, renal, metabolic, gastrointestinal, urogenital, or endocrine disorders, or other abnormalities (except for the targeted disease) that could affect study participation or the study results. Also, patients meeting any of criteria a through c below.

a. Patients with uncontrolled diabetes (HbA1c > 8% at screening). However, patients whose HbA1c is brought under control with diabetes medications may be rescreened.

b. Patients with uncontrolled hypertension (systolic blood pressure > 150 mmHg and diastolic blood pressure > 90 mmHg at 2 separate measurements taken no more than 60 minutes apart at screening). Patients whose blood pressure is brought under control by antihypertensive medication may be rescreened.

c. Patients with myocardial infarction, unstable symptomatic ischemic heart disease, arrhythmias of CTCAE Grade > 2, thromboembolism (deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events), or other heart diseases (eg, pericardial effusion, restrictive cardiomyopathy). However, chronic stable atrial fibrillation controlled by stable anticoagulant therapy will be allowed.

13. Patients with bilateral hydronephrosis or bladder neck outlet obstruction.
14. Known hypersensitivity to TAK-385, TAK-385 excipients, or GnRH antagonists.
15. Patients with a past history of gastrointestinal tract treatments (including gastrectomy) or gastrointestinal disease that could affect the drug absorption or tolerability (malabsorption, esophageal reflux, peptic ulcer, erosive esophagitis).
16. Patients positive for hepatitis B surface antigens (HBsAg), hepatitis C virus (HCV) antibodies, human immunodeficiency virus (HIV) antibodies, or serologic test for syphilis, or with life-threatening disease other than cancer, at screening.
17. Clinically relevant ECG abnormalities, or the following ECG abnormalities, at screening.

    a. Q-wave infarction, unless identified 6 or more months prior to TAK-385 treatment initiation

    b. QTcF interval > 450 msec (when calculating the QTc interval, Fridericia's equation [$QT/RR^{0.33}$] will be used)

18. Patients with congenital QT prolongation.
19. Current use of Class 1A or Class 3 antiarrhythmic medications.
20. New York Heart Association [18] Class III or IV heart failure (Appendix H).
21. Patients with clinical laboratory abnormalities suggesting clinically relevant underlying disease, or with any of the following abnormal results, at screening.

    - Serum creatinine ≥ 2.0 mg/dL
    - ALT or AST ≥ 1.5 × ULN for the investigational site
    - Total bilirubin ≥ 2 × ULN for the investigational site
    - Neutrophil count < 1,500/$mm^3$, platelet count < 100,000/µL, hemoglobin < 10.0 g/dL

- Results of heart-related tests (creatine kinase MB [CK-MB] and cardiac troponin T) exceeding the investigational sites reference value.

22. Patients found to have clinical problems on the basis of examination findings, ECG findings, or chest X-ray findings at screening.
23. Patients considered unlikely by investigators to be able to follow the study protocol or considered ineligible for the study by investigators for other reasons.

## 7.3 Prohibited Concomitant Medications, Therapies, and Foods

### 7.3.1 Prohibited Concomitant Medications

The concomitant use of the following medications will be prohibited during the treatment period out of concern for the effects on safety, PK, and pharmacodynamics. Furthermore, in Part A, the prohibited concomitant medications may not be used until the end of the post-treatment observation period.

- GnRH agonists
- GnRH antagonists
- Steroidal antiandrogens
- Nonsteroidal antiandrogens
- Drugs that include corticosteroids (except for topical drugs)
- Male sex hormone preparations
- Female sex hormone preparations
- 5α reductase inhibitors
- Docetaxel
- Other chemotherapy drugs indicated for prostate cancer
- Drugs with moderately powerful to strongly powerful CYP3A4 inhibitory or inducing effects
- Drugs with P-gp inhibitory effects

### 7.3.2 Prohibited Concomitant Therapies

The following therapies for prostate cancer will be prohibited from study treatment initiation until the end of safety follow-up.

- Surgical castration
- Prostatectomy
- High-intensity focused ultrasound therapy
- Radiotherapy

### 7.3.3 Food

From study treatment initiation and during the treatment period (in Part A, until the end of the post-treatment observation period), the use of nutritional supplements and the consumption of grapefruit and related beverages/foods will be prohibited unless judged necessary by the investigator.

## 7.4 Subject Management

1. Inpatient/outpatient status

   Subjects will be admitted to the investigational site from one day before treatment initiation in each cohort (Day -1) until Day 15 in Part A. As a rule, from Day 16 on, the study will be conducted on an outpatient basis until the safety follow-up. However, from Day 27 on, if a subject lives far from the hospital and it would be difficult for the subject to come to the hospital at the scheduled times, or if the subject desires admission, the study may be conducted on an inpatient basis from Day 27 until Day 35 at the latest. While subjects are inpatients in Part A, they will eat meals (breakfast, lunch, and dinner) at specified times. After being discharged as well, subjects will be instructed to avoid eating or drinking excessively until the end of safety follow-up. When subjects are coming in for visits on an outpatient basis, they will be instructed to be sure to eat dinner on the day before the day of a visit at which a blood sample will be collected for laboratory testing, and they will be instructed to return to the hospital on the following day without eating for blood collection and testing, after which they will receive TAK-385 and then eat breakfast at least 30 minutes later.

   If a subject desires to return home temporarily during the inpatient period, and it would not interfere with study treatment, observations, or tests, then the investigator may allow the subject to return home temporarily, after carefully checking to be sure that the subject's condition is stable, on the basis of the data that have been collected during the study to that point.

   Unless there is a special reason, Part B will as a rule be conducted on an outpatient basis. Subjects will be instructed to observe the scheduled visit times and undergo the examinations and the specified tests. Subjects will also be instructed to inform the investigator promptly if they are not able to come in for a scheduled visit.

2. Study treatment

   Investigators will instruct subjects to take the study drug 30 minutes before breakfast on each day, and to make sure that the time they take the study drug is the same on each day, to the extent possible.

   If a subject forgets to take the study drug 30 minutes before breakfast, the subject should take the drug 30 minutes before lunch on the same day. If a subject forgets to take the study drug both 30 minutes before breakfast and 30 minutes before lunch, the subject should take the study drug 30 minutes before dinner on the same day. It will be explained to subjects that they should not take any study drug that they have forgotten to take on a later day together with the study drug for that day. Subjects

will also be instructed to be sure to note in the patient diary the time they took the study drug as well as whether or not they took the study drug 30 minutes before breakfast.

On scheduled outpatient visit days, subjects will be asked to come to the investigational site in the morning without taking the study drug, and the scheduled tests will be performed.

3. Drinks, etc.

On days on which study drug is to be taken, subjects will be prohibited from drinking anything from 1 hour before dosing until 30 minutes after, other than one cup of water when they take the study drug.

4. Other

Investigators will instruct subjects that, if a subjective symptom emerges, it should be reported, along with the date of onset, severity, outcome, and date of outcome, when the subject next visits the investigational site.

Investigators will instruct subjects not to take any drugs, including over-the-counter drugs, other than the drugs that they are instructed to take, without consulting the investigator in advance.

Subjects will be instructed that, if they are treated at another medical institution in the time between the treatment period and the safety follow-up, they are to report the background for and nature of said treatment to the investigator, and to inform the medical institution in question that they are participating in a clinical study.

## 7.5 Criteria for Discontinuation or Withdrawal of a Subject

Investigators will enter into the electronic case report form (eCRF) the primary reason for discontinuation or withdrawal of the subject from the study, classified into one of the following categories. See Section 9.1.23 for subjects discontinuing before the study treatment initiation (in the case of Part A) or before randomization (in the case of Part B).

**1. Pretreatment event or adverse event**

This will be considered the primary reason if the subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE; if a serious AE occurs, the subject temporarily stops taking the study drug, and the AE recurs following study treatment resumption, or does not resolve event after 2 weeks of treatment interruption; or if toxicity that is considered DLT occurs in Part A.

- Liver function test abnormalities

If a LFT abnormality meeting any of the following criteria occurs during study treatment, study drug administration will be discontinued immediately, and appropriate follow-up tests will be performed until the subject's clinical laboratory profile returns to normal, to the level of the first test value obtained after informed

consent (in the case of a PTE), or to baseline (in the case of an AE) (see Section 9.1.8).

- ALT or AST > 3 × ULN; AND total bilirubin > 2 × ULN or PT-INR > 1.5

**2. Major protocol deviation**

This will be considered the primary reason for study withdrawal if it is discovered after the first dose of study treatment (in the case of Part A) or after randomization (in the case of Part B) that the subject does not meet the enrollment criteria specified in the study protocol, or has not followed the study protocol, and that continuing the study would pose an unacceptable risk to the subject's health.

**3. Lost to Follow-up**

This will be considered the primary reason for study withdrawal if a subject fails a study visit and cannot be contacted. In this case, the fact that contact was attempted will be noted in the source documents.

**4. Voluntary withdrawal**

This will be considered the primary reason for withdrawal if the subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE or lack of efficacy should not be recorded in the "voluntary withdrawal" category).

**5. Study termination**

This will be considered the primary reason for withdrawal if the sponsor, IRB, or regulatory authorities decide to terminate the study.

**6. Lack of efficacy**

This will be considered the primary reason for withdrawal if the expected level of efficacy is not obtained because of disease progression assessed by PSA level or evaluation of soft tissue or bone lesions by diagnostic imaging (according to the Prostate Cancer Handling Guidelines, Fourth Edition [16]), or if the decrease in serum testosterone meets any of the following criteria.

1) If, in Part A, serum testosterone does not drop below 50 ng/dL at 2 or more time points at least 7 days apart following treatment initiation, and it is determined as a result that the patient must be switched to some other therapy.

2) If, in Part B, serum testosterone does not drop below 50 ng/dL by 4 weeks after uptitration based on the uptitration criteria (see Section 8.1.3.1).

3) If, in Part B, serum testosterone exceeds 50 ng/dL on 2 consecutive occasions, or on 3 occasions in total, whether consecutive or not, by 9 weeks (57 days) after the start of treatment following uptitration in accordance with the uptitration guidelines (see Section 8.1.3.1).

## 7.6 Procedures for Discontinuation or Withdrawal of a Subject

If a subject meets the criteria described in Section 7.5, the investigator will withdraw the subject from the study. Furthermore, subjects may withdraw from the study without providing a reason at any time during the study. If a subject withdraws from the study, the investigator will enter the primary reason for withdrawal in the eCRF, and will perform all procedures scheduled for the Early Termination Visit.

# 8.0 STUDY DRUG MANAGEMENT

This section contains information regarding all study drugs provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

## 8.1 Study Drug

### 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Investigational Drug

(1) Investigational drug name: TAK-385

(2) Chemical name

*N*-(4-{1-(2,6-Difluorobenzyl)-5-[(dimethylamino)methyl]-1,2,3,4-tetrahydro-3-(6-methoxypyridazin-3-yl)-2,4-dioxothieno[2,3-*d*]pyrimidin-6-yl}phenyl)-*N*'-methoxyurea

(3) Dosage forms and doses

- TAK-385 40 mg tablets: Each tablet contains 40 mg as TAK-385
- TAK-385 80 mg tablets: Each tablet contains 80 mg as TAK-385

There are two types of study drug, described above; both are light red, film-coated tablets.

(4) Packaging and labeling

Each dosage form comes packaged 40 tablets to a bottle. The label clearly states that the drug is for use in a clinical study, and also bears the drug name, protocol number, name and address of the study sponsor (or company that manufactured the drug), manufacturing number, and storage method (Figure 8.a).

For Use in a Clinical Study
TAK-385 40 mg Tablets (or 80 mg Tablets)
For oral administration
Contains 40 tablets
Protocol number: TAK-385/TB-AK160108
Manufacturing number: ●●●●●●●
Storage method: Room temperature (1-30°C)
Expiration date: See the study drug control procedures
Unused study drug and used bottles will be collected by the study sponsor; do not discard.

**Takeda Pharmaceutical Company**
4-1-1 Doshomachi, Chuo-ku, Osaka

**Figure 8.a Sample TAK-385 Bottle Label**

8.1.1.2 Drugs not Provided by the Study Sponsor

No drugs will be provided other than the study drug and drugs such as GnRH agonists and/or GnRH antagonists following the completion (or discontinuation) of TAK-385 administration.

### 8.1.2 Storage

TAK-385 will be stored at room temperature (1-30°C).

Investigational drug must be stored in an appropriate, limited-access, secure place until they are used or until they are returned to the sponsor or a designee for destruction. Investigational drug must be stored under the conditions specified on the label, and must remain in their original containers until dispensed. The daily temperature log of the drug storage area must be maintained every working day.

### 8.1.3 Dose and Regimen

Table 8.a shows the dosage and number of tablets in Part A (by cohort), and Table 8.b shows the dosage and number of tablets in Part B (by treatment group).

**Table 8.a Cohorts, Dosages, and Numbers of Tablets (Part A)**

| Cohort | Dosage/Number of Tablets |
|---|---|
| 1 | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 80 mg (Days 2 to 28): One 80 mg tablet per day |
| 2 | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 120 mg (Days 2 to 28): One 80 mg tablet and one 40 mg tablet per day |
| 3 | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 160 mg (Days 2 to 28): One 80 mg tablet and two 40 mg tablets per day |
| Additional cohort[*1] | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 40 mg (Days 2 to 28): One 40 mg tablet per day |

*1: Added if tolerability is not confirmed in Cohort 2

**Table 8.b Treatment Groups, Dosages, and Numbers of Tablets (Part B)**

| Treatment Group | Dosage/Number of Tablets |
|---|---|
| 80 mg | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 80 mg (Day 2 to Week 48[*3]): Two 40 mg tablets per day |
| 120 mg | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 120 mg (Day 2 to Week 48[*3]): One 80 mg tablet and one 40 mg tablet per day |
| 40 mg[*2] | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 40 mg (Day 2 to Week 48[*3]): One 40 mg tablet per day |
| At uptitration | One TAK-385 40 mg tablet per day will be added |

*2: If no problems with tolerability are found in the additional cohort in Part A
*3: Treatment may be continued for up to 96 weeks in total

The specified dose of TAK-385 will be taken once a day orally with 1 cup of water at least 30 minutes before breakfast. Except for when various tests are being performed or an AE occurs, an effort will be made to ensure that subjects rest for 2 hours after receiving the dose.

The investigator or study support staff will check to make sure that all specified study drug has been taken.

#### 8.1.3.1 Criteria for Upward Dose Adjustments

Part A: The dose of TAK-385 will not be increased even if inadequate testosterone suppression occurs (< 50 ng/dL). If after treatment initiation the serum testosterone level does not drop below 50 ng/dL at 2 or more time points separated by at least 7 days and the investigator or sub-investigator determines that the patient needs to be switched to some other treatment, then TAK-385 treatment will be stopped and the patient withdrawn from the study.

Part B: If the following conditions are met, the dose may be adjusted, taking efficacy and safety into consideration. Dose adjustment will be performed when the subject is examined by the investigator or sub-investigator.

If the serum testosterone level in an individual patient exceeds 50 ng/dL at Week 5 (Day 29), Week 9 (Day 57), or Week 13 (Day 85), following review of compliance, a one-time upward dose modification (increment of 40 mg daily) will be allowed. After Week 13, the dose will not be increased even if the serum testosterone level exceeds 50 ng/dL.

The dose will not be increased in the 120 mg group before the DLT evaluations have been completed for Cohort 3 in Part A, or if the dose has not been found to be tolerable. Similarly, if tolerability is not found in Cohort 2 in Part A and a 40 mg group is therefore going to be used instead of a 120 mg group, then the dose in the 80 mg group will not be increased.

#### 8.1.3.2 Criteria for Dose Holds and Dose Reduction

Part A: If a treatment-related AE occurs, or if it would be difficult to continue with TAK-385 treatment, then the dose of TAK-385 will not be reduced, and study treatment will be interrupted if necessary.

Part B: If a treatment-related AE occurs or if it would be difficult to continue with TAK-385 treatment, then study treatment will be interrupted if necessary. Subjects who experience serious AEs requiring study treatment interruption within 12 weeks (84 days) following treatment initiation may have their doses reduced by one dose level – 40 mg – following a 2-week treatment interruption period. If the AE continues even after dose reduction, or the subject's serum testosterone level exceeds 50 ng/dL for 4 to 6 weeks following dose reduction, then TAK-385 treatment will be discontinued so that the subject may receive some other therapy. If a serious AE requiring study treatment interruption occurs on or after Week 13 (Day 85) following treatment initiation, and the subject's treatment has not been interrupted prior to that, then the subject's treatment may be interrupted for 2 weeks and then resumed. However, if the AE recurs following study treatment resumption, or if the AE does not resolve even after 2 weeks of treatment interruption, then the subject will be withdrawn from the study.

Even if the dose has been increased in accordance with Section 8.1.3.1, when reducing the dose, it will be reduced by one dose level. Dose reduction will not be performed for subjects in the 40 mg group. In addition, if the dose is reduced in accordance with this section, then the dose may not be increased as described in Section 8.1.3.1.

Furthermore, if a LFT abnormality is found, it will be handled as shown in Table 8.c.

**Table 8.c Guidelines for Handling Liver Function Test Abnormalities**

| Category | ALT, AST, and Total Bilirubin | Study Drug | ALT and AST Tests | Treatment Interruption | Dose Adjustment |
|---|---|---|---|---|---|
| A | ALT or AST ≥ 1.5 × ULN to < 3 × ULN<br>AND<br>Total bilirubin < 1.5 × ULN | Continue without changing the dose | Perform tests every week for 2 weeks, and then every 2 weeks for 4 weeks until stable[*1] | Not necessary | Not necessary |
| B | ALT or AST ≥ 3 × ULN to < 5 × ULN<br>AND<br>Total bilirubin < 1.5 × ULN | Continue without changing the dose | Perform tests every week, and then every 2 weeks for 4 weeks until stable[*1] | Not necessary | Not necessary |
| C | ALT or AST ≥ 5 × ULN to < 8 × ULN<br>AND<br>Total bilirubin < 1.5 × ULN | Interrupt treatment | Perform 2 tests in the first week, then every week for 2 weeks, and then every 2 weeks until stable[*1] | Interrupt treatment until stable[*1] | Reduce the TAK-385 dose to 40 mg |
| D | ALT or AST ≥ 8 × ULN to < 20 × ULN<br>AND<br>Total bilirubin <1.5 × ULN | Interrupt treatment | Perform 2 tests a week for the first 2 weeks, and then every 2 weeks until stable[*1] | Interrupt treatment until stable[*1] | Reduce the TAK-385 dose to 40 mg[*2] |
| E | ALT or AST ≥ 3× ULN<br>AND<br>Total bilirubin > 2 × ULN<br>(Hy's law) | Permanently discontinue treatment | Perform 2 tests a week until the test values drop, and then every week until stable[*1] | N/A | N/A |

*1: Stable means ALT and AST both CTCAE Grade 1 (> ULN to 3 × ULN)
*2: The study sponsor should be consulted before resuming treatment.

### 8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.

Serious AEs associated with overdose should be reported according to the procedures outlined in Section 10.2.2.

In the event of a study drug overdose, the investigator will treat the subject symptomatically.

## 8.2 Study Drug Allocation and Prescribing Procedures

In Part A, in order to confirm eligibility for study participation based on the screening tests, the investigator or a person designated by the investigator will contact the registration center by fax. The investigator will prescribe study drug to the subject after confirming that the subject is eligible for the study based on a fax received from the registration center.

In Part B, the investigator or a person designated by the investigator will contact the registration center by fax to confirm the subject's eligibility at the start of the treatment period. After confirming, on the basis of a fax received from the registration center, that the subject is eligible, the investigator will prescribe the subject the study drug for the group to which the subject has been assigned. The investigator or a person designated by the investigator will enter the group to which the subject has been assigned in the eCRF.

Subjects will be assigned a 4-digit number, with the first signifying the Part and Cohort, the second signifying the investigational site, and the last two digits constituting a series number within the cohort at the investigational site. This 4-digit number will be used by the investigational sites to identify the specimens that will be used to assess the PK and pharmacodynamics. These numbers will be noted on the specimen tubes that are provided for measurement, and will be used instead of the subject identification numbers for reporting the measurement results. These numbers will not be replaced by the last 3 digits of the subject identification numbers.

## 8.3 Randomization Code Creation and Storage

The randomization manager (or a person designated by the study sponsor) will prepare a randomization table. The randomization information will be stored in a safe location, and will only be accessible to authorized personnel.

## 8.4 Control and Disposal of Drugs Provided by the Study Sponsor

The study drug controller will receive the written procedures prepared by the study sponsor specifying the handling, storage, and control of study drug, and will appropriately control the drugs provided by the study sponsor in accordance with these written procedures. The investigators will also receive these procedures from the study sponsor. These procedures will describe the procedures that will have to be followed to ensure that the receipt, handling, storage, control, and prescribing of the study drugs provided by the study sponsor, as well as the recovery of unused drugs from subjects and their return to the study sponsor, or their disposal, are carried out appropriately and reliably.

The study drug controlled will promptly return to the study sponsor any unused drugs once the study has been completed at the investigational site in question.

# 9.0 STUDY PLAN

## 9.1 Study Proceduress

The following sections describe the study procedures and data to be collected. In principle, the same investigator will perform examinations and testing, observations, and evaluations of subjects. The Schedule of Study Procedures is shown in Appendix A to Appendix E.

### 9.1.1 Informed Consent

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained from the subject before any protocol-directed procedures are performed.

A unique subject identification number will be assigned to each subject at the time that informed consent is explained. The same subject number will be used throughout the study.

**Informed Consent for Pharmacogenomics**

Informed consent for the storage and banking of the blood sample for pharmacogenomics (PGx) testing in this study must be obtained separately before collection. The provision of consent to collect and analyze the PGx sample is independent of consent to the other aspects of the study.

### 9.1.2 Demographics, Medical History, and Treatment History

Demographic data will include date of birth, sex, and smoking history at screening. The items listed below will be checked with regard to prostate cancer [16]. The findings will be input to the eCRF.

- Date of diagnosis and diagnostic method used
- Gleason classification (pattern 1 to 5 and score) at most recent assessment and date of assessment
- Tissue type and extent of differentiation
- Treatment history (including medication history)
- TNM classification (at time of diagnosis)
- Prostatectomy yes/no, total resection yes/no, date of surgery
- High intensity focused ultrasound yes/no, completion date
- Radiation therapy yes/no, completion date
- History of other therapy yes/no, mode of therapy, start date, completion date

The medical history will include clinically relevant diseases or conditions associated with the targeted disease that disappeared or ended within the past 1 year from the date of

informed consent. If a symptom or disease is still present, it will be considered a comorbidity (concurrent medical condition) (see Section 9.1.18).

Previous therapeutic drugs used (medication history) will include all drugs that were discontinued within 28 days before the date of informed consent and are relevant to the eligibility criteria.

### 9.1.3 Physical Examination

A physical examination will be conducted for the parts of the body listed below (interview, visual inspection, auscultation, palpation, percussion, etc.).

(1) eyes, (2) ears, nose, and throat, (3) cardiovascular system, (4) respiratory organs, (5) digestive organs, (6) skin, (7) extremities, (8) musculoskeletal system, (9) nervous system, (10) lymph nodes, (11) urogenital organs, (12) other

The investigator will evaluate abnormal findings discovered in the pre-administration physical examination for clinical relevance and record the results in the source data. Findings and changes considered to be clinically relevant will be input as PTEs or comorbidities at the proper locations in the source data and eCRF as described in Sections 10.0 and 9.1.18.

### 9.1.4 Weight, Height, and ECOG Performance Status

Weight and height will be measured. Weight will be measured in kilograms to the first decimal place, and height will be measured in centimeters to the closest integer. In addition, the ECOG performance status will be measured in accordance with Appendix G.

### 9.1.5 Vital Signs

Measurement of vital signs will include temperature (axillary), seated blood pressure (systolic and diastolic after resting at least 5 min) and heart rate (bpm). Measurements will be taken after the subject has been sitting for 5 min.

### 9.1.6 Electrocardiogram

A 12-lead ECG will be performed. Measurements will be taken after the subject has been in supine position for 5 min. The investigator (or a specialist at the medical institution) will assess the results by the following categories: Normal range ("Within Normal Limits"), Abnormal but not clinically significant ("Abnormal, Not Clinically Significant "), or Abnormal and clinically significant ("Clinically Significant ").

The following parameters will be transferred from the subject's ECG recording to the eCRF: heart rate, QT interval, PR interval, QRS duration, and RR interval.

In determining the QTc value, Bazett corrected QT (QTcB) and QTcF will be calculated using the Bazett formula ($QT/RR^{0.5}$) and Fridericia formula ($QT/RR^{0.33}$), respectively.

### 9.1.7 Imaging Assessment

CT or MRI (thoracic, abdominal, and pelvic regions) and bone scintigraphy will be performed during screening to verify that there are no distant metastatic lesions. If

measurements were taken within 28 days before the start of study drug administration, the results of diagnostic imaging and tests conducted before obtaining informed consent can be used. CT or MRI and bone scintigraphy will also be performed on the days stipulated in the clinical trial schedule (Appendix A to Appendix C) to check for new lesions. Disease progression will be determined by the presence or absence of new lesions based on the items evaluated in diagnostic imaging. Diagnostic imaging will also be performed as needed in Part A if abnormal findings appear in other tests and examinations during administration of the study drug.

### 9.1.8 Clinical Laboratory Tests

Specimens will be handled according to the procedures described in a separate document. A general guideline for the total amount of blood to be collected in this study is shown in Section 9.5.

Samples for clinical laboratory tests will be collected after at least 10 hours of fasting on the days stipulated in the Schedule of Study Procedures (Appendix A to Appendix E). Samples to be collected for each laboratory test are shown in Table 9.a.

**Table 9.a Clinical Laboratory Tests**

| Hematology | Chemistry | Metabolic Panel | Urinalysis |
|---|---|---|---|
| RBC | Total protein | Triglycerides | pH |
| WBC | Albumin | Total cholesterol | Specific gravity |
| Hemoglobin | Glucose | HDL cholesterol | Protein (qualitative) |
| Hematocrit | Creatinine | LDL cholesterol | Glucose (qualitative) |
| Platelet count | BUN | TSH | Occult blood (qualitative) |
| Differential WBC (neutrophils [including absolute count], basophils, eosinophils, lymphocytes, monocytes) | Uric acid | HbA1c | Ketones (qualitative) |
| | Total bilirubin | | Urobilinogen (qualitative) |
| | ALT | | Bilirubin (qualitative) |
| | AST | | |
| | LDH | | |
| | γ-GTP | | |
| | ALP | | |
| | CK (CPK) | | |
| | Na | | |
| | K | | |
| | Cl | | |
| | Ca | | |
| | P | | |
| | PT-INR | | |
| **Tests to be conducted when determining eligibility** | | | |
| (to be performed only when deemed necessary) | | | |
| HIV test; hepatititis tests including HBsAg and anti-HCV; serologic test for syphilis | | | |

The above clinical laboratory tests will be performed at the medical institution. The investigator will evaluate and archive reported clinical laboratory test findings.

When the ALT or AST levels are > 3 × ULN, retesting (at least ALP, ALT, AST, total bilirubin, γ-GTP, and PT-INR) will be performed within 48 to 72 hours (within 7 days at the latest).

(See Section 7.5 for the criteria for the withdrawal from the study. See Section 10.2.3 for the reporting of LFT abnormalities in cases where the ALT or AST level exceeds 3 × ULN, and the total bilirubin level exceeds 2 × ULN or the PT-INR exceeds 1.5.)

The investigator will archive the reference ranges for the clinical laboratory tests, including the history.

All clinically relevant, abnormal laboratory test values will be input in the source data and eCRF of the subject as AEs, etc. All clinically relevant, abnormal laboratory test values verified by retesting will be followed up in all subjects until the abnormal value returns to an acceptable level or there is a sufficient explanation for the observed change.

### 9.1.9 Cardiac Tests

CK-MB and cardiac troponin T will be measured at the institution during screening. These measurements will also be performed as needed when abnormal findings appear in other tests and examinations during administration of the study drug.

### 9.1.10 Tumor Marker

PSA will be measured by a third-party organization according to a separately prepared written procedure. Progression of disease as indicated by PSA (based on the Prostate Cancer Handling Guidelines, 4th Edition [16]) is defined as an increase of at least 25% in the PSA value measured at least 4 weeks after the minimum PSA value measured during the study period (at least 12 weeks if the minimum value was recorded during screening). In such a case, the amount of increase must be at least 2 ng/mL. The date this condition is met will be considered the disease progression date.

### 9.1.11 Collection of Pharmacogenomic Sample

After the start of study drug administration (Part A) or after randomization (Part B), one sample for PGx testing will be collected as early as possible during the administration period. A sample of 5 mL of whole blood for DNA extraction will be collected in an EDTA-treated polypropylene tube from each subject who has given consent. The sample will be sent to the sample storage facility.

Details of collection, handling, and storage of the sample for PGx testing will be carried out according to a separately prepared written procedure.

### 9.1.12 Bone Mineral Density (Part B Only)

Bone mineral density will be measured by dual-energy X-ray absorptiometry (DXA). Throughout the study period the same subject will be measured on the same model of equipment using the same scanning mode. The investigator will input the equipment model, date of measurement, and results for the following measurement parameters into the eCRF.

Measurement sites: Lumbar 2 to 4 (L2 to L4) and hip (femoral neck, femoral trochanteric, femoral intertrochanteric, Ward's triangle, and total)

Measurement parameters: Bone mineral content (BMC, g), bone area (Area, $cm^2$), and bone mineral density (BMD, $g/cm^2$) of L2, L3, and L4, femoral neck, femoral trochanteric, and femoral intertrochanteric regions, and Ward's triangle; and total bone mineral content (BMC, g) (combined), bone area (Area, $cm^2$) (combined), and bone mineral density (BMD $g/cm^2$) (Mean) of L2 to L4 and hip.

### 9.1.13 Ophthalmological Examination (Part B Only)

The examination will be carried out in a darkened room. A slit lamp microscope will be used to examine the anterior of the eye, and the results will be classified as follows: Normal range, Abnormal but not clinically significant, or Abnormal and clinically significant.

### 9.1.14 BMP Concentrations (Part B Only)

BMP will be measured in serum and urine samples by a third-party organization according to a separately prepared written procedure. Sequential BMP testing will not be performed, and the measurements will be summarized after a fixed time period. Measurements will be conducted when there are clinical findings suggesting an association with phospholipidosis or there is a report of an association between comparable GnRH antagonists and phospholipidosis.

### 9.1.15 QOL Assessment (Part B Only)

QOL will be assessed using AMS, EORTC-QLQ-C30, and EPIC scores. After arriving at the hospital each subject will personally fill in the form provided by the sponsor before other tests are conducted and before the study drug is administered. The scoring of QOL will be carried out in the order: AMS, EORTC-QLQ-C30, and EPIC.

### 9.1.16 Concomitant Medications

The term concomitant medication is refers to any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through safety follow-up), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

### 9.1.17 Concomitant Therapies

The term concomitant therapy refers to a medical act carried out for a therapeutic purpose. At each study visit, subjects will be asked whether they have received any therapeutic procedures (performed from signing of informed consent through safety follow-up).

### 9.1.18 Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at screening examinations. The details of the condition (ie, diagnosis) should be recorded in the eCRF.

### 9.1.19 Contraception

Male subjects with female partners who may become pregnant will use a barrier-type contraceptive device (eg, condom and spermicidal cream or jelly) from the time of informed consent until 4 months after the final dose of the study drug. Furthermore, the subject will be instructed not to donate sperm during this time frame.

### 9.1.20 Pregnancy

If the subject's female partner becomes pregnant, the investigator, with the female partner's consent, will inform her attending physician (obstetrician) that the subject was participating in a clinical study when she became pregnant and reveal the details of the study drug.

If a pregnancy is reported for any subject, the investigator, with the subject's consent, will carry out a follow-up investigation until delivery, including premature delivery, and make a report to the sponsor using the designated follow-up form. The investigator will also conduct a postnatal evaluation.

### 9.1.21 Pharmacokinetic Assessments

The plasma concentrations will be measured at each blood sample collection time point (see Appendix D and Appendix E) in accordance with separately prepared written procedures.

The 3 time points for TAK-385 dosing that immediately precede blood sample collection, and the time points for the collection of blood samples for pharmacokinetic assessment, will be entered into the eCRF.

### 9.1.22 Pharmacodynamic Assessments

Serum testosterone, LH, FSH, DHT, and SHBG will be measured by an external measurement facility in accordance with separately prepared written procedures. Serum testosterone will be measured along with other highly sensitive measurements at specified time points (see Appendix B). Detailed information about the treatment and shipment of samples will be provided in the aforementioned written procedures as well.

### 9.1.23 Documentation of Subjects Withdrawing From the Study Prior to Study Treatment Initiation or Prior to Randomization

The principal investigators will be responsible for all subjects who sign informed consent. Investigators will prepare eCRFs for all subjects who withdraw from the study prior to study treatment initiation or randomization.

The primary reason for withdrawal from the study prior to study treatment initiation (in the case of Part A) or prior to randomization (in the case of Part B) will be entered into the eCRF based on the following categories.

- PTE / AE
- Does not meet inclusion criteria or meets exclusion criteria < The reason will be entered. >
- Major deviation from the study protocol
- Follow-up impossible
- Spontaneous withdrawal < The reason will be entered. >
- Entire study discontinued
- Other < The reason will be entered. >

The subject identification numbers of subjects withdrawing from the study will not be reused.

### 9.1.24 Documentation of Study Enrollment/Randomization

In Part A, only subjects who meet all of the inclusion criteria and do not meet any of the exclusion criteria will be enrolled in the treatment period. If a subject cannot proceed to the treatment period, the investigator will enter the primary reason for this in the eCRF.

In Part B, only subjects who meet all of the inclusion criteria and do not meet any of the exclusion criteria will be randomized. If a subject cannot be randomized, the investigator will enter the primary reason for this in the eCRF.

## 9.2 Monitoring Subject Treatment Compliance

During the inpatient period in Part A, the investigator or a person designated by the investigator will give the subject the study drug, confirm that the subject has taken it, and record this in the source documents. For study drug administration following discharge from the investigational site, subjects will be instructed to take the drug appropriately.

On the day of the first dose in Part B, the investigator or a person designated by the investigator will administer the study drug to the subject, confirm that the subject has taken the drug, and record this in the source documents. For study drug administration from Day 2 on, subjects will be instructed to take the drug appropriately.

The day of treatment initiation, the day of treatment completion, the dose, the actions taken with respect to the dose, and the reasons for any changes will be entered in both the source documents and the eCRF.

Subjects will be instructed to bring their study drug (bottles) in with them at each outpatient visit. If it is found that a subject has not complied with the study treatment in the time since the previous visit (eg, if 20% [6 doses] or more of the specified doses have not been taken), then the subject may be withdrawn from the study. If the subject is given instructions about treatment noncompliance, then this will be recorded in the source documents.

## 9.3 Schedule of Observations and Procedures

Appendix A through Appendix E show the schedules for all tests, observations, and assessments. Investigators will perform the tests, observations, and assessments shown below at the specified time points.

### 9.3.1 Screening

Observations and tests will be performed within 28 days prior to the first dose of study drug to confirm subject eligibility for study participation based on the inclusion and exclusion criteria presented in Section 7.0. See Section 9.1.23 for the preparation of records for subjects withdrawing from the study during screening.

The following tests, observations, and assessments will be performed at screening.

- Informed consent
- Demographics, medical history, concurrent medical condition, treatment history
- Physical examination
- Vital signs
- Weight, height, and BMI
- ECOG performance status
- HBsAg, HCV, and HIV antibody and serologic test for syphilis
  If the institutional review board judges it necessary, these tests will be performed only for subjects determined by the investigator to be at high risk for hepatitis B or C or HIV infection.
- 12-lead ECG
- Chest X-ray examination
- Imaging assessments
- Clinical laboratory tests (hematology, chemistry, metabolic panel, and urinalysis)
- Cardiac tests
- Pharmacodynamic assessments (serum testosterone, LH, FSH, DHT, and SHBG)
- Tumor marker (PSA)
- Concomitant medications
- Concomitant therapies
- PTEs

The following tests will be performed only in Part B.

- Ophthalmological examinations
- Bone mineral density
- QOL assessments

### 9.3.2 Study Enrollment/Randomization

In Part A, subjects will be enrolled into each cohort by the day before study treatment initiation on the basis of the results of the aforementioned screening.

In Part B, subjects will be randomized by the day before study treatment initiation on the basis of the results of the aforementioned screening.

Subject who meet all of the inclusion criteria and do not meet any of the exclusion criteria will be enrolled or randomized in accordance with Section 8.2. As described in Section 9.2, subjects will receive their first dose of study drug at the investigational site under the supervision of the investigator or a person designated by the investigator.

### 9.3.3 Day of Study Treatment Initiation

The following tests, observations, and assessments will be performed before study drug is administered on the day of study treatment initiation. If 12-lead ECG or clinical laboratory tests were performed at screening up to 3 days prior to treatment initiation, then they may be used as the tests performed prior to treatment initiation.

- Physical examination
- Vital signs
- Weight
- 12-lead ECG
- Clinical laboratory tests (hematology, chemistry, metabolic panel, and urinalysis)
- Pharmacokinetic assessments

The following tests will be performed only in Part B

- Pharmacodynamic assessments (only serum testosterone by high-sensitivity measurement)
- BMP concentrations
- QOL assessments

### 9.3.4 Study Drug Treatment Period (Except for the Day of Study Treatment Initiation)

During the study treatment period, physical examinations and tests will be performed at scheduled inpatient and outpatient time points. The following tests, observations, and assessments will be performed during the treatment period.

- Physical examination
- Vital signs
- Weight
- ECOG performance status
- 12-lead ECG
- Imaging assessments
- Clinical laboratory tests (hematology, chemistry, metabolic panel, urinalysis)
- Pharmacodynamic assessments (serum testosterone, LH, FSH, DHT, and SHBG)
- Tumor marker (PSA)
- PGx sample collection
- Concomitant medications
- Concomitant therapies
- AEs
- Treatment compliance
- Pharmacokinetic assessments

The following tests will be performed only in Part B

- Ophthalmological examinations
- Bone mineral density
- BMP concentrations
- QOL assessments

### 9.3.5 Post-treatment Observation Period (Performed Only in Part A)

In Part A, the following tests, observations, and assessments will be performed as post-treatment observations for 7 days following the last dose of study drug, and the results will be entered in the eCRF. Even if the subject withdraws from the study during Part A, the same post-treatment observations may be performed, depending on the subject's treatment status. If a subject withdraws from the study, this will be reported to the study sponsor, which will be consulted about what actions should be taken.

- Physical examination
- Pharmacodynamic assessments
- Pharmacokinetic assessments
- Concomitant medications
- Concomitant therapies
- AEs

### 9.3.6 Continuation Treatment Period

In Part B, if a subject continues receiving the study drug after 48 weeks, the following tests, observations, and assessments will be performed every 12, 24, or 48 weeks.

- Physical examination
- Vital signs
- Weight
- ECOG performance status
- 12-lead ECG
- Imaging assessments
- Clinical laboratory tests (hematology, chemistry, metabolic panel, and urinalysis)
- Pharmacodynamic assessments (serum testosterone, LH, FSH, DHT, and SHBG)
- Tumor marker (PSA)
- Concomitant medications
- Concomitant therapies
- AEs
- Treatment compliance
- Bone mineral density
- QOL assessments

### 9.3.7 At Study Withdrawal

If a subject withdraws from the study, the reason for withdrawal will be entered in the source documents and the eCRF, and the following tests, observations, and assessments will be performed within 8 days, including the day of withdrawal. In Part B, if a subject withdraws from the study (before Week 96), these same tests, observations, and assessments will be performed. The status of completion of the study will be entered in the eCRF for all subjects who received study drug in Part A, and for all subjects randomized in Part B. Furthermore, in Part B, if a subject completes 48 weeks of treatment, but does not subsequently continue receiving study drug, then the subject's status of study completion (including the reason treatment was not continued) will be entered in the eCRF.

- Physical examination
- Vital signs
- Weight
- ECOG performance status
- 12-lead ECG

- Imaging assessments
- Clinical laboratory tests (hematology, chemistry, metabolic panel, and urinalysis)
- Pharmacodynamic assessments (serum testosterone, LH, FSH, DHT, and SHBG)
- Tumor marker (PSA)
- Concomitant medications
- Concomitant therapies
- AEs
- Treatment compliance
- Pharmacokinetic assessments (depending on the time of withdrawal)

The following tests will be performed only in Part B.

- Ophthalmological examination (except for subjects who withdraw from the study after advancing to the continuation treatment period)
- Bone mineral density
- BMP concentrations (except for subjects who withdraw from the study after advancing to the treatment continuation period)
- QOL assessments

### 9.3.8 Safety Follow-up

The following tests, observations, and assessments will be performed as safety follow-up 30 to 40 days after the day of the last dose of study drug, and will be the final observations performed.

These same tests, observations, and assessments will be performed 30 to 40 days after the last dose of study drug for subjects who withdraw from the study as well.

The status of study completion will be entered into the eCRF for all subjects who receive study drug in Part A, and for all subjects who are randomized in Part B.

- Physical examination
- Vital signs
- Weight
- ECOG performance status
- 12-lead ECG
- Clinical laboratory tests (hematology, chemistry, metabolic panel, and urinalysis)
- Concomitant medications
- Concomitant therapies
- AEs

The following tests will be performed only in Part B.

- QOL assessments

### 9.3.9 Handling After the End of the Study

Study drug will not be supplied to subjects who have completed the study treatment period and the continuation treatment period (Part B).

## 9.4 Biological Sample Storage and Disposal

The 5 mL samples of whole blood collected for PGx research will be stored frozen at the sample storage facility (Protocol Annex 1).

The storage period will be 20 years from the day the samples for PGx research were initially collected in this study.

During the sample storage period, if a subject wants his samples destroyed, the investigational site will ask, via the study sponsor, and in accordance with the specified procedures, the sample storage facility to destroy the subject's samples. The sample storage facility will destroy the samples in questions in accordance with the procedures, and will inform the investigational site and the study sponsor that the samples have been destroyed. However, if the data that allow the subject to be identified (eg, medical records) have been destroyed once the study has been completed, and it is therefore no longer possible to link the subject to his samples, then the samples will not be destroyed.

Even if the samples can be tied to the subject, if the PGx investigation has already been performed, the remaining samples will be destroyed, but the anonymized results of the PGx investigation will be retained by the study sponsor.

The study sponsor will construct the administrative structure necessary to protect subjects' personal information, and will stipulate in advance criteria for handling sample collection, storage, and disposal, as well as prepare the necessary written procedures.

## 9.5 Blood Sample Volumes and Numbers of Samples Collected

Table 9.b, Table 9.c, and Table 9.d present guidelines for the volumes of blood samples to be collected for each subject.

**Table 9.b Blood Sample Volumes and Numbers of Samples Collected (Part A)**

| Type of Sample | Volume of Blood Collected Per Sample (mL) | Number of Samples (Times) Collected | Total Volume (mL) |
|---|---|---|---|
| Hematology tests | 12 | 7 | **84** |
| Chemistry tests | 9.2 | 7 | **64.4** |
| Metabolic panel tests | 5.6 | 4 | **22.4** |
| Cardiac tests | 4.4 | 1 | **4.4** |
| Tumor marker | 2.0 | 2 | **4** |
| HIV, etc. tests*1 | 5.6 | 1 | **5.6** |
| Pharmacodynamic assessments | 7.0 | 9 | **63** |
| PGx sample collection | 5 | 1 | **5** |
| PK assessments | 3 | 37 | **111** |
| **Total Volume of Blood Collected** | | | **363.8** |

*1: Will be performed only when judged necessary

**Table 9.c Blood Sample Volumes and Numbers of Samples Collected (Part B – Screening Through Week 48, Safety Follow-up)**

| Type of Sample | Volume of Blood Collected Per Sample (mL) | Number of Samples (Times) Collected | Total Volume (mL) |
|---|---|---|---|
| Hematology tests | 12 | 9 | **108** |
| Chemistry tests | 9.2 | 15 | **138** |
| Metabolic panel tests | 5.6 | 8 | **44.8** |
| Cardiac tests | 4.4 | 1 | **4.4** |
| Tumor marker | 2.0 | 9 | **18** |
| BMP concentrations | 2 | 5 | **10** |
| HIV, etc. tests*1 | 5.6 | 1 | **5.6** |
| Pharmacodynamic assessments | 7.0 | 13 | **91** |
| Serum testosterone (high-sensitivity measurement) | 5 | 11 | **55** |
| PGx sample collection | 5 | 1 | **5** |
| PK assessments | 3 | 15 | **45** |
| | | **Total Volume of Blood Collected** | **524.8** |

*1: Will be performed only when judged necessary

**Table 9.d Blood Sample Volumes and Numbers of Samples Collected (Part B – Weeks 49 to 96)**

| Type of Sample | Volume of Blood Collected Per Sample (mL) | Number of Samples (Times) Collected | Total Volume (mL) |
|---|---|---|---|
| Hematology tests | 12 | 4 | **48** |
| Chemistry tests | 9.2 | 4 | **36.8** |
| Metabolic panel | 5.6 | 4 | **22.4** |
| Tumor marker | 2.0 | 4 | **8** |
| Pharmacodynamic assessments | 7.0 | 4 | **28** |
| | | **Total Volume of Blood Collected** | **143.2** |

# 10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

## 10.1 Definition

### 10.1.1 Pretreatment Events

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

### 10.1.2 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug (including study drug); it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

### 10.1.3 Additional Points to Consider for Pretreatment Events and Adverse Events

An untoward findings generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre existing conditions underlying disease should not be considered PTEs or AEs.)
- Require therapeutic intervention
- Require an invasive diagnostic procedure
- Require discontinuation or a change in dose of study drug or concomitant medication
- Be considered unfavorable by the investigator for any reason.

Diagnosis vs signs and symptoms:
Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) and/or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:
Change in laboratory value or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required, or if the investigators judges the change to be beyond the normal physiological fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation, or monitoring of an abnormality is not considered an intervention.

If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal impairment), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions (disease or symptoms existing before informed consent is obtained):
Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Abnormalities found in initial tests and observations (eg, laboratory tests, ECG, and radiology) after informed consent should NOT be recorded as PTEs unless related to study procedures, except that abnormalities occurring as a result of initial test or observation procedures (such as internal bleeding during blood draw) will be recorded as PTEs in the eCRF. If the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of hypertension").

If a subject has a pre-existing episodic condition (eg, asthma, epilepsy) that increase in frequency or become serious or severe should be recorded as PTEs/AEs. Symptoms that worsen more than expected in subjects with chronic disease (eg, cataracts, rheumatoid arthritis) should also be recorded as PTEs/AEs. Investigators should ensure that the AE term recorded captures the changes in the condition from Baseline (eg, "worsening of XX").

Worsening of PTEs or AEs:
If the subject experiences a worsening or complication of a PTE after starting administration of the study drug or experiences signs/symptoms that occur secondarily to PTEs, the worsening or complication should be recorded appropriately as an AEs in the eCRF. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of XX").

If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE in the eCRF. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of XX").

Underlying disease:
In this study, worsening of the underlying disease will not be handled as an AE. The onset or worsening of symptoms associated with progression of the underlying disease will be handled as an AE.

Planned surgeries or procedures:
Preplanned procedures (surgelies or therapies) that were scheduled prior to signing of informed consent were not considered PTEs or AEs, except that any conditions and events associated with the worsening of pre-existing conditions requiring those procedures to be undertaken on an emergency basis should be captured appropriately as a

PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:
Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):
Insufficient clinical response, efficacy, or pharmacological effect should NOT be recorded as an AE. Investigators must make a distinction between worsening of preexisting symptoms and lack of efficacy.

Overdose:
Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but overdoses will be recorded on an overdose page of the eCRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

### 10.1.4 Serious Adverse Events

A serious AE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE-THREATENING*.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

* The term "life threatening" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.

**Table 10.a Takeda Medically Significant AE List**

| | |
|---|---|
| Acute respiratory failure/acute respiratory distress syndrome | Hepatic necrosis |
| Torsade de pointes/ventricular fibrillation/ventricular tachycardia | Acute hepatic failure |
| Malignant hypertension | Anaphylactic shock |
| Convulsive seizures (such as convulsions and epilepsy) | Acute renal failure |
| Agranulocytosis | Pulmonary hypertension |
| Aplastic anemia | Pulmonary fibrosis (including interstitial lung disease) |
| Toxic epidermal necrolysis/oculomucocutaenous syndrome (Stevens-Johnson syndrome) | Neuroleptic malignant syndrome/malignant hyperthermia |
| | Spontaneous abortion/stillbirth and fetal death |
| | Confirmed or suspected transmission of infectious agent by drugs |
| | Confirmed or suspected endotoxic shock |

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported by the same procedures as for SAEs (see Sections 10.2.2 and 10.3).

### 10.1.5 Special Interest Adverse Events

A special interest AE (whether serious or not) is one of specific and medical concern specific to the study drug or program. Investigators will monitor subjects on an ongoing basis for such events, and the sponsor will be notified immediately of any that occur. Further investigation may sometimes be necessary to establish assessment of these events. Refer to Section 10.2.1.3 for the methods and deadlines for reports to the sponsor by investigators.

#### 10.1.5.1 Liver Function Test Abnormalities

LFT abnormalities were identified as specific AEs because nonclinical studies in monkeys revealed LFT abnormalities and because clinical studies on oral GnRH antagonists with the same backbone structure as TAK-385 have revealed elevated AST and ALT as common treatment-related AEs.

The management of LFT abnormality AEs is presented in Table 8.c of the protocol. When ALT or AST levels are > 3 × ULN, retesting will be performed within 48 to 72 hours (within 7 days at the latest). As soon as they become aware that ALT or AST levels are > 3 × ULN, investigators will discuss detailed information on affected subjects and other potential causes with the sponsor to review whether the administration of study drug should be discontinued immediately.

If ALT or AST levels are > 3 × ULN and total bilirubin levels are > 2 × ULN or the PT-INR is > 1.5, and investigators conclude that the levels cannot be explained by any factor other that study drug based on the results of retesting, then they will be handled as serious AEs.

When LFT abnormalities correspond to the criteria in Section 7.5, investigators will immediately discontinue administration of study drug and will perform appropriate follow-up.

### 10.1.6 Severity of Pretreatment Events and Adverse Events

The severity of AEs, including laboratory abnormalities, will be determined according to the CTCAE. Events not covered in the CTCAE will be classified and defined as follows.

| | |
|---|---|
| Grade 1 | Mild;[*1] asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated |
| Grade 2 | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[*2] |
| Grade 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limited self care ADL[*3] |
| Grade 4 | Life-threatening consequences; urgent intervention indicated |
| Grade 5 | Death related to AE |

*1: A semi-colon indicates 'or' within the description of the grade.
*2: Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
*3: Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

AEs that undergo a change in severity for the worse will be individually recorded in the eCRF as separate AEs.

Clarification should be made between a serious AE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event, but the event itself may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as "serious." For example, a white blood cell count of 1000 to 2000/$mm^3$ is considered Grade 3 (severe) but may not necessarily be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

### 10.1.7 Causality of Adverse Events

The relationships of each AEs to study drug will be assessed using the following categories:

| | |
|---|---|
| Related | An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concomitant therapies, may also be responsible. |
| Not related | An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concomitant therapies. |

### 10.1.8 Relationship to Study Procedures

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

### 10.1.9 Date of Onset

The date of AE onset (the start date of the AE/PTE) will be determined based on the following criteria.

| AEs | Date of onset |
|---|---|
| Signs, symptoms, disease (diagnosis) | The date on which the subject or investigators first notice the signs or symptoms of an AE will be recorded. |
| Asymptomatic disease | The date on which a diagnostic test is conducted and the diagnosis is confirmed will be recorded.<br>The date on which diagnosis is confirmed will be recorded even when test findings belatedly reveal older findings or when the time of onset can be generally estimated. |
| Worsening of complications or PTEs | The date on which the subject or investigators first notice worsening of signs or symptoms will be recorded. |
| When initial test results after informed consent are normal but subsequent test results are abnormal (PTE)<br>When test results turn abnormal after start of study drug treatment (AEs) | The date on which laboratory abnormalities considered clinically significant are found will be recorded. |
| When test results after informed consent are initially normal but then worsen (PTE)<br>When test results at start of study drug treatment are abnormal and then worsen (AE) | The date of tests on which laboratory profiles reveal clear increases or decreases based on clinical judgment. |

### 10.1.10 Date Resolved

The date resolved (the stop date of the AE/PTE) is the date on which AEs resolve (including resolved with sequelae). When AEs result in death, the date of death will be used. When an AE is recorded as a separate AE in the eCRF due to worsening of severity, the day before the date on which worsening was confirmed will be recorded as the date of resolution. Cases in which resolution cannot be confirmed at the end of the study will be assessed as ongoing.

### 10.1.11 Frequency

When an AE that apparently resolves and occurs repeatedly (such as constipation, diarrhea, and vomiting) is determined by investigators to be a series of occurrences constituting a single event over the period of time from initial onset to ultimate resolution, the incidence will be considered "intermittent." All other cases will be handled as "continuous."

### 10.1.12 Action Taken for Study Drug

Actions taken for study drug will be classified and defined as follows.

| | |
|---|---|
| Drug Withdrawn | A study drug is terminated due to the particular AE (including when subjects themselves decide to discontinue). |
| Dose not Changed | The particular AE did not require any dose change of study drug.<br>Discontinuation of study drug, dose reduction, or dose escalation due to AE other than the AE in question will be handled as "dose not changed."<br>Discontinuation of study drug or dose reduction for reasons other than action taken for the AE, such as subject carelessness, will be handled as "dose not changed." |
| Unknown | When subjects cannot be contacted and the course after the date of onset cannot be ascertained, etc. |
| Not Applicable | When study drug treatment has already been completed or discontinued at the time that the AE occurs |
| Dose Reduced | A reduction in study drug dose as action taken for the AE will be handled as "dose reduced"(the dose cannot be reduced at the subject's discretion) |
| Dose Increased | An escalation in study drug dose as action taken for the AE will be handled as "dose increased"(the dose cannot be escalated at the subject's discretion) |
| Dose Interrupted | A temporary discontinuation (suspension) of study drug as action taken for the AE followed by the resumption of dosing on a later date (including when subjects themselves decide to temporarily discontinue) will be handled as a "dose interrupted." |

### 10.1.13 Outcome

The outcome of AEs will be classified as follows:

| Classification | Criteria |
|---|---|
| Recovered/ Resolved | • Symptoms or findings resolve or recover<br>• Test results normalize or return to levels at baseline (AEs) or to levels at informed consent (PTEs)<br>• When an event is recorded as a separate AE due to worsening severity in the eCRF |
| Recovering/ Resolving | • Severity decreases at least 1 grade<br>• Symptoms and findings are nearly resolved<br>• Test results are improved, but have not normalized or returned to levels at baseline (AEs) or to levels at informed consent (PTEs)<br>• The subject died from a cause other than the particular AE/PTE with the condition remaining “recovering/resolving”. (the date of death does not need to be recorded in such cases) |
| Not Recovered/ Not Resolved | • No change in symptoms, findings, or test results<br>• Symptoms, findings, or test results on last observable day are worse than at onset<br>• Irreversible congenital anomaly/birth defect<br>• The subject died from a cause other than the particular AE/PTE with the particular AE/PTE state remaining “Not recovered/not resolved”. (the date of death does not need to be recorded in such cases) |
| Resolved, with Sequelae | • Occurrence of dysfunction interfering with ADL |

| Classification | Criteria |
|---|---|
| Fatal | • Death immediately related to AEs<br>• "Immediately related" indicates that the AEs caused death or were clearly involved in the death.<br>• Outcomes such as for AEs that are not determined (concluded, assumed) to have been the immediate cause of death in the same subject will not be handled as death.<br>• The date of death will be recorded when the outcome is death. |
| Unknown | • Follow-up of the event cannot be performed as specified in the protocol because of transfer to another hospital, change in residence, or the like |

## 10.2 Procedures

### 10.2.1 Collection and Reporting of Adverse Events

#### 10.2.1.1 Collection Period of Pretreatment Events and Adverse Events

Pretreatment events will be recorded continuously from when informed consent is obtained until the first dose of study drug (Day 1). If it is decided that a subject should be withdrawn before the first dose of study drug, PTEs will be recorded until that point in time.

AEs will be recorded continuously from the start of study drug administration to subjects (Day 1) until the safety follow-up.

#### 10.2.1.2 Reporting of Adverse Events

Investigators will check for subjective symptoms whenever subjects visit. Investigators will ask subjects about AEs that may have occurred since the last visit by asking questions such as "How have you been since the last visit?"

Any subjects who experience a PTE that meets the criteria for seriousness will be followed up by investigators until symptoms resolve or until medically significant laboratory abnormalities return to initial levels after informed consent, or else (in the case of a permanent or irreversible PTE) until the observed change can be satisfactorily explained. No protocol follow-up will be required for PTEs that do not meet the criteria for seriousness, regardless of the causal relationship to study procedure.

Any subjects who experience an AE will be followed up by investigators until symptoms resolve or until medically significant laboratory abnormalities return to initial levels after informed consent, or else (in the case of a permanent or irreversible AE) until the observed change can be satisfactorily explained, regardless of the causal relationship to study drug. All AEs will be recorded in the eCRF. The following information will be documented for each event: event term, start and stop dates, frequency, severity (intensity), causal relationship to study drug (related, not related), action taken on study drug, outcome, causal relationship to study procedures (and procedure considered the cause if causally related), and seriousness.

AEs, and PTEs meeting the criteria for seriousness, will be followed up until the AE/PTEs resolve or until investigators determine that no further follow-up is needed.

10.2.1.3 Reporting of Special Interest Adverse Events

When an AE of special interest that occurs during the period for recording AEs is determined to be medically significant based on the following criteria, investigators will report the event to the sponsor (see attachment for contact information) within 24 hours of the onset of the AE of special interest or within 24 hours after learning of the event from the subject. The principal investigator will also prepare a report of LFT abnormalities (same report form as for SAEs) within 10 business days, and submit it with a signature or printed name and personal seal to the contact identified in the attachment.The "Liver Function Test Abnormality Reporting Checklist (Appendix I)" will be used as reference to assist in the preparation of the report.

The criteria for LFT abnormalities are given below:
• ALT or AST > 3 × ULN

If ALT or AST levels are > 3 × ULN and total bilirubin levels are > 2 × ULN or the PT-INR is > 1.5, and investigators conclude that the levels cannot be explained by any factor other that study drug based on the results of retesting (for procedures, see Section 10.1.5.1), then they will be handled as serious AEs, and information will be recorded and reported by the procedures noted in Section 10.2.2.

AEs of special interest will be recorded as AEs in the eCRF. Related information (such as photographs, results of additional diagnostic tests, and records of consultations with specialists) will also be submitted to the sponsor.

### 10.2.2 Collection and Reporting of Serious Adverse Events

SAEs that occur in the period for recording AEs will be reported by the following procedures. PTEs meeting the criteria for seriousness noted in Section 10.1.4 will be reported by the same procedure as SAEs.

All SAEs that occur from the start of study drug administration in subjects until the safety follow-up will be reported by the principal investigator to the sponsor within 24 hours of confirming or being notified of the event. The initial report of an SAE and all revised or additional information will be recorded in an "SAE Report" to be submitted to the sponsor. Copies of related source documentation on medical treatment of subjects will be submitted to the sponsor as soon as possible. In cases of death, a copy of the autopsy report will be submitted, if possible.

Even after the end of the study, treatment-related SAEs will be reported to the sponsor within 24 hours of confirming or being notified of the event.

SAEs leading to withdrawal from the study or discontinuation of study drug will be recorded in initial or subsequent "SAE Reports" and in the eCRF.

As a general rule, the initial report of an SAE will be faxed to the Safety Information Emergency Response Center using the prescribed "Report of an SAE [Initial Report]" form. After faxing the form, the principal investigator will submit the original to the monitors.

After the initial report of the SAE, the principal investigator will report detailed information to the sponsor within 10 calendar days. As a general rule, the detailed information will be faxed to the Safety Information Emergency Response Center using the prescribed "Report of SAEs (Detailed Information)" form. After faxing the form, the principal investigator will submit the original to the monitors. Any modifications of the contents of the report will be similarly reported.

Safety Information Emergency Response Center (24 hours a day, 365 days a year)
[redacted]
*FAX :* [redacted]
*TEL :* [redacted]

When the Safety Information Emergency Response Center cannot be contacted, the information will, as a general rule, be reported to the monitors using the prescribed "Report of an SAE [Initial Report]" form or "Report of SAEs (Detailed Information)" form.

All SAEs occurring onsite will be reported by the principal investigator to the head of the investigational site by the established procedures in force at the investigational site and to the sponsor in accordance with this protocol.

The expectedness of SAEs will be determined on the basis of the Investigator's Brochure (including information on AEs reported to investigational site).

### 10.2.3 Reporting of Drug-Induced LFT Abnormalities Potentially Leading to Severe Liver Disorders

Investigators will report ALT or AST levels > 3 × ULN to the sponsor and will promptly investigate detailed subject information and potential causes other than study drug (presence or absence of acute viral hepatitis type A or B, or other acute liver diseases, medical history, and complications). Retesting will also be performed (see Section 10.1.5). If ALT or AST levels are > 3 × ULN and total bilirubin levels are > 2 × ULN or the PT-INR is > 1.5, and investigators conclude that the levels cannot be explained by any factor other that study drug, the information will be reported by the same procedure for SAEs (see Section 10.2.1.3).

## 10.3 Follow-up of Serious Adverse Events

If information not reported in the detailed report becomes available at a later date, investigators will record the information on a copy of the SAE report or will prepare a separate document, and one or the other will be submitted to the contact identified in the attachment. Investigational site-related data (such as ECG findings, laboratory findings, summary of report of discharge from hospital, and results of autopsy) will be submitted upon request to the sponsor or the IRB.

Investigators will follow-up all SAEs until they resolve or until the final outcome is determined.

### 10.3.1 Reporting of Serious Adverse Events to Principal Investigators, IRB, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and other SAEs subject to expedited reporting to the regulatory authorities, principal investigators, and the IRBs/head of the investigational site in accordance with the local regulations of the counties in which the study is being conducted. The sponsor or the sponsor's CRO will submit an expedited report of fatal or life-threatening SUSARs within 7 days, and of any other serious events within 15 days, of first learning of or obtaining additional information on the event to the regulatory authorities. The sponsor will also submit an expedited report of other safety issues potentially having a significant effect on the benefit-risk assessment of study drug, continuation of study drug treatment, or continuation of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB.

## 11.0 STUDY SPECIFIC COMMITTEES

A SMC will be established in this study. The principal duties of the SMC will be to decide when cohorts can progress to the next Part or to make the necessary decisions when it is difficult to judge whether or not DLTs have occurred. This is described in detail in separately prepared procedures.

## 12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary [generic term] and the Japanese Drug Dictionary.

### 12.1 Electronic Case Report Form

Completed eCRFs are required for each subject who signs informed consent.

The sponsor or its designee will supply the investigational site with access to the eCRF system. The sponsor will make arrangements to train the investigators and appropriate study support staff in use of the eCRF system. The eCRFs will be used to transmit the information collected during the study to the sponsor and regulatory authorities. The eCRF must be completed in English. Data will be directly recorded onto eCRF.

The following will be recorded as an audit trail when changes or revisions are made in the eCRF: the original and changed/revised information, person making the change or revision, and the date and reasons for the change or revision.

The principal investigator must review the eCRFs for completeness and accuracy, and must electronically sign the appropriate page of the eCRF. The principal investigator bears full responsibility for the accuracy and reliability of all data recorded in the eCRFs.

The following data will not be directly recorded in the eCRF.

1) Tumor marker, BMP concentration, and pharmacodynamic parameters (except for SHBG) measured by an external measurement facilities.

2) Plasma drug concentration results

Investigators will use the eCRF change and revision record (Data Clarification Form) provided by the sponsor when changing or revising recorded entries in the eCRF after the clinical trial database has been locked. The principal investigator must review the data change for accuracy and completeness, and must provide a signature or printed name and personal seal, and the date.

The sponsor or its designee will check the accuracy and completeness of the eCRF when visiting the investigational site. The sponsor or its designee will be permitted to review subject's medical and hospital records related to the study to ensure the accuracy of the eCRFs. Completed eCRFs are the property of the sponsor, and should not be made available in any form to third parties other than regulatory authorities without the written permission of the sponsor.

### 12.2 Record Retention

The principal investigator or head of the investigational site will keep the following records, including the records and study-specific documents specified in Section 12.1. These materials will include the identification log of all participating subjects, medical records, source worksheets, all original signed and dated informed consent forms,

electronic copies of the eCRFs including audit trail, and drug accountability log. The essential relevant documents that are to be archived must also be kept by the principal investigator and head of the investigational site until the day specified as 1) or 2) below, whichever comes later, unless the sponsor requires records to be kept for longer periods of time than this, in which case the head of the investigational site will reach agreement on the retention period and record keeping methods with the sponsor.

1) The day on which marketing approval of the investigational drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2) The day 3 years after the date of early termination or completion of the clinical study.

The principal investigator and head of the investigational site will also keep the essential relevant documents that are to be archived until notified by the sponsor that the records no longer need to be kept.

# 13.0 STATISTICAL METHODS

## 13.1 Statistical and Analytical Plans

Analysts will prepare and finalize the Statistical Analysis Plan before database lock. The Statistical Analysis Plan will describe in detail the definitions of the endpoints and analytical methods in order to meet all study objectives.

Data review will take place before database lock. The accuracy and completeness of the study data, the evaluability of subjects, and the appropriateness of the planned analysis will be assessed during data review.

### 13.1.1 Analysis Sets

Four populations for analysis will be established in this study: the full analysis set, the safety analysis set, the DLT analysis set, and the pharmacokinetic analysis set. The safety analysis set will be defined as all subjects who receive at least 1 dose of any study drug. The DLT analysis set will be defined as all subjects who can be evaluated for DLTs (see Section 6.1.2.3). The analysis sets will be defined in detail in the separately prepared "Rules for Handling Analytical Data."

Before database lock, the sponsor will consult the medical expert as needed to check on the appropriateness of the analysis set definitions and rules for handling the analysis of the case data in the sets, and will finalize the "The Rules for Handling Analytical Data" after deciding how to handle problematic issues not specified at the planning stage.

### 13.1.2 Analysis of Demographics and Other Baseline Characteristics

The primary subject characteristics in the safety analysis set will be tabulated. Descriptive statistics (number of subjects, mean, median, standard deviation, maximum, minimum, and quartiles [same below]) will be calculated for continuous data, and frequency tabulations of discrete data will be prepared.

### 13.1.3 Efficacy Analysis

[Secondary endpoint]

PSA (Part B)

[Analytical method]

The full analysis set will be analyzed as follows.

1) PSA

Descriptive statistics and the two-sided 95% confidence interval of the mean for PSA in Part B will be calculated at each assessment time point specified in the protocol, and the changes over time (individual and mean/SD) will be graphed by dose. The changes from baseline will also be similarly analyzed. Waterfall plots of the change from baseline at Week 13 Day 1 (LOCF) and the change from baseline for the minimum value after the start of study drug treatment will be prepared by dose.

2) Data conversion and handling of missing data

PSA levels below the lower limit of quantification will be handled as the LLOQ. Test data that is not assessed or that is missing, or that is not used per the "Rules for Handling Analytical Data," will be excluded from the analysis of assessment.

[Other endpoints]

- PSA (Part A)
- Disease progression as assessed on the basis of PSA, disease progression as assessed on the basis of image assessment (Part B)

### 13.1.4 Pharmacokinetic Analysis

[Secondary endpoint]

Plasma concentration of unchanged TAK-385

[Analytical method]

The pharmacokinetic profile (such as Cmax and AUC) will be calculated by model-free analysis of the plasma concentration profiles of unchanged TAK-385 in the pharmacokinetic analysis set. Descriptive statistics of each parameter will be calculated by Part and by dose. Descriptive statistics for the plasma concentration of TAK-385 at each blood sampling time point specified in the protocol will also be calculated by dose, and the changes over time (individual and mean) will be graphed by dose. The plasma concentration profiles of TAK-385 will also be analyzed using a compartment model as needed.

### 13.1.5 Pharmacodynamic Analysis

[Secondary endpoint]

Serum testosterone concentration

[Analytical method]

The full analysis set will be analyzed as follows.

1) Serum testosterone concentration

Descriptive statistics and the two-sided 95% confidence interval of the mean for serum testosterone concentration will be calculated by Part and by dose at each assessment time point specified in the protocol, and the changes over time (individual and mean/SD) will be graphed by Part and by dose.

2) Data conversion and handling of missing data

Test parameters below the lower limit of quantification will be handled as the LLOQ. Test data that is not assessed or that is missing, or that is not used per the "Rules for Handling Analytical Data," will be excluded from the analysis of assessment.

[Other endpoints]

Serum concentrations of LH, FSH, DHT, and SHBG

### 13.1.6 Other Analysis

[Other endpoints]

QOL assessment based on AMS, EORTC-QLQ-C30, and EPIC (Part B)

### 13.1.7 Safety Analysis

[Primary endpoints]

DLTs, AEs, clinical laboratory tests, vital signs, and 12-lead ECG

[Analytical methods]

1) Adverse events

The following analysis will be performed for the safety analysis set.

A treatment-emergent adverse event (TEAE) refers to an event that occurs after the start of study drug administration.

The following TEAE will be tabulated by Part and by dose. TEAEs will be coded according to MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT).

- Frequency tabulations of all TEAEs
- Frequency tabulations of treatment-related TEAEs
- Frequency tabulations of all TEAEs by severity
- Frequency tabulations of treatment-related TEAEs by severity
- Frequency tabulations of TEAEs for which the study drug action taken was "treatment discontinuation"
- Frequency tabulations of serious TEAEs
- Frequency tabulations of all TEAEs by time of onset

2) DLT

The following analysis will be performed for the DLT analysis set.

Frequency tabulations of TEAEs determined to be DLTs in Part A will be tabulated by PT and by dose.

3) Clinical laboratory tests, vital signs, and 12-lead ECG

The following analysis will be performed for the safety analysis set.

For continuous data, descriptive statistics for observed values at baseline and at each assessment time point as well as for the change from baseline will be calculated by part and by dose.

Cross tables for the results of the assessment of each test parameter based on discrete data and reference values before and after study drug treatment (such as the determination of

whether results are normal or abnormal, or qualitative laboratory values) will be prepared by part and by dose.

[Other endpoints]

- Bone mineral density

### 13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

### 13.3 Determination of Planned Sample Size

[Part A]

Each cohort will have 3 or 6 subjects, based on the guidelines on the clinical evaluation of antineoplastics.

[Part B]

In order to detect less frequent AEs, 15 subjects per group (total of 30 subjects) were established as the number of cases enabling an approximately 80% chance of detecting AEs characterized by a true incidence of 10%.

# 14.0 QUALITY CONTROL AND QUALITY ASSURANCE

## 14.1 Monitoring of Investigational Site

Monitoring visits to the investigational site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee and by the IRB.

The sponsor or its designee will access the principal investigator's files, medication, medical records of subjects, and records such as the informed consent form to ensure that the study is being properly conducted in compliance with the protocol. They will also confirm the consistency of the eCRFs with related source documents. Investigators and other study support staff members will take the time to accommodate monitors when they visit the investigational site for monitoring purposes.

## 14.2 Protocol Deviations

Investigators may deviate from or modify the protocol without the prior written agreement of the sponsor or prior approval of the IRB for medically unavoidable circumstances, such as to avoid immediate hazards to subjects. On such occasions, the principal investigator will inform the sponsor and head of the investigational site in writing of the details of and reasons for the deviation or change, will keep copies of the notification, and will reach agreement with the sponsor on protocol revisions as needed. If the protocol is to be revised, a draft will be submitted as soon as possible to the head of the investigational site, and the approval of the IRB will be required.

Investigators should document all deviations from the protocol.

## 14.3 Quality Assurance Audits and Regulatory Authority Inspections

The sponsor or designee will audit the investigational site as needed. On such occasions, an auditor designated by the sponsor will contact the investigational site beforehand to schedule the auditing visit. The auditor may ask to visit the facilities where laboratory test samples are kept, the facilities where medication is stored and prepared, and other facilities used during the study. During this study, inspections may also be carried out by regulatory authorities, including overseas agencies (such as the US Food and Drug Administration [FDA] and the UK Medicines and Healthcare Products Regulatory Agency [MHRA]). The sponsor will be notified immediately whenever the investigational site receives a request for an inspection by the regulatory authorities. The principal investigator and head of the investigational site will ensure that the auditor has access to all study-related documentation set forth in Section 14.1.

## 15.0 ETHICAL ASPECTS OF THE STUDY

This trial will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and International Conference on Harmonisation (ICH) Guidelines for GCP. Investigators will conduct the study in accordance with regional regulatory requirements and the "Responsibilities of the Principal Investigator" in Appendix F.

### 15.1 IRB Approval

The IRB must be will be constituted according to the applicable local regulations in regions participating in the study. The sponsor or designee will obtain documentation of the names and affiliations of the IRB members. When IRB members directly participate in the study, documentation that they are not involved in the review and decision-making process must be obtained.

The sponsor or designee will submit related documents to the IRB for review and approval of the protocol. In addition to the study protocol, Investigator's Brochure and copies of the informed consent as well as materials and advertising related to the recruitment of subjects, if needed, and other documents required by local regulations must also be submitted to central or local IRBs for approval. The sponsor or designee will obtain documented approval of the protocol and informed consent form by the IRB before the start of the study (i.e., before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will ship drug after confirming the appropriateness of the documented regulations of the investigational site. Until the site receives drug, no protocol activities, including screening may occur.

The investigational site will follow all requirements specified by the IRB. This includes notifications to the IRB regarding protocol amendments, updates to the informed consent form, revisions of materials related to subject recruitment, reports on safety required by local regulatory requirements, periodic reports on the conduct of the study as stipulated by the IRB, and the study completion report. The sponsor or designee will obtain all documented IRB approval of the above and related materials.

Financial compensation paid to subjects should be kept to a level that will not provide undue incentive to participate in the study. Financial relief must be approved by the IRB and sponsor.

PGx analysis of collected and stored samples will perform at the time when the details have been decided. At that time, the sponsor will prepare a PGx protocol, and the protocol will require prior approval of the sponsor.

### 15.2 Patient Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form will describe the

planned and permitted use (either in Japan or abroad: submission to third parties) and disclosure of the personal information and personal medical information of subjects in this study. The informed consent form will further explain the nature of the study, objectives, and of the potential risks and benefits. The informed consent form will also detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care. The principal investigator is responsible for the preparation and contents of the informed consent form, and for obtaining the approval of the IRB. The informed consent form must be approved by the IRB before being used.

The informed consent form must be written in a language fully comprehensible to the prospective subject. Investigators will be responsible for providing subjects with a detailed explanation of the contents of the informed consent form. Information should be provided verbally and in writing by a method deemed suitable by the IRB whenever possible.

Investigators will give subjects (1) a chance to ask questions about the study and (2) enough time to decide whether to participate in the study. Subjects who decide to participate in the study will personally sign and date the informed consent form before participating in the study. Investigators will ask subjects to use a black or blue ball point pen to sign the form using their full legal names. Investigators will also sign and date the informed consent form before the subject can participate in the study.

Investigators will keep the signed original informed consent form. The date on which subjects sign the informed consent form will be recorded by investigators in the medical records of the subjects. Subjects will be given a copy of the signed informed consent form.

If the informed consent form is revised, investigators will again obtain the informed consent of the subjects using the same procedures that were used to obtain initial consent. The date on which informed consent is again obtained will be recorded in the medical records of the subjects, and subjects will be given a copy of the revised informed consent form.

Subjects who have received an explanation of the study based on the informed consent form will be given an explanation of PGx analysis based on the "Informed Consent Form for PGx Analysis in the TAK-385 Study." Specimens for PGx analysis will be obtained from subjects who sign both the informed consent for the study and the informed consent for PGx analysis.

The procedure in Section 9.4 will be followed whenever subjects would prefer their stored samples to be disposed of.

### 15.3 Subject Confidentiality

The sponsor or designee affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique subject identification number. As permitted by all applicable laws and regulations, limited

subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (such as the FDA, MHRA, and PMDA), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, the subject's name, address, and other identifier fields not collected on the subject's eCRF).

## 15.4 Publication, Disclosure, and Clinical Trial Registration Policy

### 15.4.1 Publication and Disclosure

The principal investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During the study, except when required by laws or regulations, only the sponsor may disclose study information to other investigators or regulatory authorities. Except where otherwise permitted by the Clinical Study Agreement, any public disclosure of the protocol and study results (including public websites) is the responsibility of the sponsor.

The sponsor may publish any data or information obtained from the study (including data and information provided by the principal investigator) without the consent of the principal investigator.

Investigators need to obtain the prior written permission of the sponsor to publish any information obtained from the study, such as to a professional associations.

### 15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on a public website (JAPIC-CTI) before the start of the clinical trial. The sponsor's contact information will be registered for general access along with the city, state (in the USA), and country where the trial is being conducted as well as subject recruitment status.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the

caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

### 15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on a public website (JAPIC-CTI), as required by applicable laws and/or regulations, regardless of the results.

## 15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or its designee will obtain clinical study insurance against the risk of injury to clinical study subjects.

Refer to the Clinical Study Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or its designee.

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## Appendix A Schedule of Study Procedures (Part A)

| Procedure[a] | Subject consent[b] | Screening | Treatment Period[c] | | | | | | | | | | Post-treatment Observation Period[d] | | | | Withdrawal[e] | SFU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Inpatient[f] | | | | | | | | Outpatient | | | | | | | |
| | | Before treatment initiation D -28 to D -1[g] | D1[h] | D2 | D3 | D7 | D12 | D13 | D14 | D15 | D21 | D28 | D29 | D30 | D31 | D35[i] | | 30 to 40 days after the last dose |
| Allowable visit window | | | 0 | | | | | | | | ± 1 | 0 | 0 | + 3 | + 3 | 0 | + 7 | |
| Confirmation of eligibility | | X | | | | | | | | | | | | | | | | |
| Subject background[j] | | X | | | | | | | | | | | | | | | | |
| Physical examination | | X | X | X | X | X | | | X | | X | X | X | X | X | X | X | X |
| Vital signs[k] | | X | X | | | X | | | X | | X | X | | | | | X | X |
| Weight/height[l] | | X | X | | | X | | | X | | X | X | | | | | X | X |
| ECOG performance status | | X | | | | | | | | | | X | | | | | X | X |
| 12-lead ECG[m] | | X | X[o] | | | | | | X | | | X | | | | | X | X |
| Chest X-ray examination | | X | | | | | | | | | | | | | | | | |
| Imaging assessment[n] | | X | Measure as appropriate | | | | | | | | | | | | | | | |
| Hematology tests | | X | X[o] | | | X | | | X | | X | X | | | | | X | X |
| Blood biochemistry tests | | X | X[o] | | | X | | | X | | X | X | | | | | X | X |
| Blood lipid, sugar, etc. tests | | X | X[o] | | | | | | | | | X | | | | | X | X |
| Urinalysis | | X | X[o] | | | X | | | X | | X | X | | | | | X | X |
| Heart-related tests | | X | Measure as appropriate | | | | | | | | | | | | | | | |
| Pharmacodynamic assessments | | X | | X | X | X | | | X | | X | X | | | X | X | X | |
| Tumor marker | | X | | | | | | | | | | X | | | | | X | |
| Pharmacokinetic assessments[p] | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[q] | |
| PGx sample collection | | | X (during the treatment period) | | | | | | | | | | | | | | | |
| Concomitant medications/ therapies | | Collected from the time of informed consent until 30 to 40 days after the last dose | | | | | | | | | | | | | | | | |
| Adverse events, etc. | PTEs[r] | | Information collected from study treatment initiation until 30 to 40 days after the last dose | | | | | | | | | | | | | | | |
| Study treatment | | | Oral doses once a day at least 30 minutes before breakfast | | | | | | | | | | | | | | | |

Abbreviations: D = Day; ECOG = Eastern Cooperative Oncology Group; PGx = pharmacogenomics; SFU = safety follow-up

a Unless otherwise specified, the assessments will be completed before study drug dosing.
b Except for procedures that are normally part of a physical examination, subjects must sign the informed consent form before any study-related procedures are performed.
c Additional examinations/assessments may be performed at the discretion of the investigator or sub-investigator.
d Days 27 to 35 are performed either on an outpatient or an inpatient basis.
e Unnecessary if the subject withdraws between Day 29 and Day 35.
f Day 1: Day of treatment initiation. As a rule, subjects will not be allowed to leave the investigational site or return home during the inpatient period. However, the investigator or sub-investigator may allow the subject to return home temporarily.
g Day -1: Day before treatment initiation
h Day 1: Day of treatment initiation
i If a subject is going to be switched to a GnRH agonist or a GnRH antagonist, this will be done after PK analysis sample collection and assessments have been completed.
j Including past and current medical history and previous therapeutic medications
k Measurements will be taken after the subject has been sitting down for 5 minutes.
l Height will be measured only at screening.
m 12-lead ECG measurements will be taken after the subject has been lying down for at least 5 minutes.
n Performed at screening only if imaging assessments were not performed within 28 days prior to treatment initiation, or if no usable images are available for the subject.
o Results of tests performed up to 3 days before treatment initiation may be used at the D1 test results.
p See Appendix D for detailed collection times.
q As a rule, blood samples will be collected at subject withdrawal as well, but the blood samples corresponding to the post-treatment observation period will not be necessary.
r Collected from consent acquisition until study treatment initiation.

## Appendix B Schedule of Study Procedures (Part B – Screening to Week 48, SFU)

| Procedure[a] | Informed consent[b] | Screening | Treatment Period[cd] | | | | | | | | | | | | | | | | | Withdrawal | SFU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Day | | Before treatment initiation[e] D -28 to D -1[f] | WK 1 D1[h] | WK 1 D2 | WK 1 D4 | WK 2 D1 | WK 3 D1 | WK 5 D1 | WK 9 D1 | WK 13 D1 | WK 17 D1 | WK 21 D1 | WK 25 D1 | WK 29 D1 | WK 33 D1 | WK 37 D1 | WK 41 D1 | WK 45 D1 | WK 49[g] D1 | | 30 to 40 days after the last dose |
| Allowable visit window | | | 0 | 0 | 0 | ±1 | ±1 | ±2 | ±2 | ±2 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±7 | +7 | |
| Confirmation of eligibility | | X | | | | | | | | | | | | | | | | | | | |
| Subject background[i] | | X | | | | | | | | | | | | | | | | | | | |
| Physical examination | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Vital signs[j] | | X | X | | | X | X | X | X | X | | | X | | | | | | X | X | X |
| Weight/height[k] | | X | X | | | X | X | X | X | X | | | X | | | | | | X | X | X |
| ECOG performance status | | X | | | | | | X | | | | | X | | | | | | X | X | X |
| 12-lead ECG[l] | | X | X[n] | | | | X | X | | | | | X | | | | | | X | X | X |
| Chest X-ray examination | | X | | | | | | | | | | | | | | | | | | | |
| Ophthalmology tests | | X | | | | | | | | | | | X | | | | | | X | X | |
| Imaging assessment[m] | | X | | | | | | | | | | | | | | | | | X | X | |
| Bone density (DXA method) | | X | | | | | | | | | | | X | | | | | | X | X | |
| Hematology tests | | X | X[n] | | | | | X | X | X | | | X | | | X | | | X | X | X |
| Blood biochemistry tests | | X | X[n] | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood lipid, sugar, etc. tests | | X | X[n] | | | | | X | X | X | | | X | | | | | | X | X | X |
| Urinalysis | | X | X[n] | | | | | X | X | X | | | X | | | | | | X | X | X |
| Heart-related tests | | X | Measure as appropriate | | | | | | | | | | | | | | | | | | |
| Pharmacodynamic assessments | | X | X[o] | X | X | X[o] | X[o] | X[o] | X[o] | X[o] | X[o] | X[o] | X[o] | | | X[o] | | | X[o] | X | |
| Tumor marker | | X | | | | | | X | X | X | X | X | X | | | X | | | X | X | |
| BMP concentration[p] | | | X | | | | | | X | | | | X | | | X | | | X | X | |
| Pharmacokinetic assessments[q] | | | X | X | X | X | X | X | X | X | X | X | X | | | X | | | X | X[r] | |

| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PGx sample collection | | | X (randomization through the treatment period) | | | | | | | | | | | | | | | | | |
| QOL assessments | | X | X | | | | | X | X | X | | X | X | | | | | X | X | X | X |
| Concomitant medications/ therapies | | Collected from the time of informed consent until 30 to 40 days after the last dose | | | | | | | | | | | | | | | | | | |
| Adverse events, etc. | | PTEs[s] | Information collected from study treatment initiation until 30 to 40 days after the last dose | | | | | | | | | | | | | | | | | |
| treatment | | | Oral doses once a day at least 30 minutes before breakfast | | | | | | | | | | | | | | | | | |

Abbreviations: WK = Week; D = Day; ECOG = Eastern Cooperative Oncology Group; PGx = pharmacogenomics; QOL = quality of life; SFU = safety follow-up

a Unless otherwise specified, the assessments will be completed before study drug dosing.
b Except for procedures that are normally part of a physical examination, subjects must sign the informed consent form before any study-related procedures are performed.
c Additional examinations/assessments may be performed at the discretion of the investigator or sub-investigator.
d Except for pharmacokinetic assessments, if the assessment and test results can be obtained, then the assessments will be performed before study treatment initiation.
e Randomization will be performed by Day -1 (1 day before treatment initiation)
f Day -1: Day before treatment initiation
g If a subject is going to be switched to a GnRH agonist or a GnRH antagonist, this will be done after PK analysis sample collection and assessments have been completed.
h Day 1: Day of treatment initiation
i Including past and current medical history and previous therapeutic medications
j Measurements will be taken after the subject has been sitting down for 5 minutes.
k Height will be measured only at screening.
l 12-lead ECG measurements will be taken after the subject has been lying down for at least 5 minutes.
m Performed at screening only if imaging assessments were not performed within 28 days prior to treatment initiation, or if no usable images are available for the subject.
n Results of tests performed up to 3 days before treatment initiaion may be used as the D1 test results.
o Blood samples will also be collected for the serum testosterone high sensitivity measurements. However, at WK1D1, only the high-sensitivity measurements will be performed.
p Blood and urine sample collection
q See Appendix E for detailed sample collection times
r As a rule, blood samples will also be collected at withdrawal from the study.
s Information will be collected from consent acquisition until treatment initiation.

## Appendix C Schedule of Study Procedures (Part B – Weeks 49 to 96)

| Procedure[a] | Continuation Treatment Period[b] | | | | | Withdrawal | SFU |
|---|---|---|---|---|---|---|---|
| Scheduled Day | WK49 (WK48) D1 (D8) | WK61 D1 | WK73 D1 | WK85 D1 | WK97[c] D1 | | 30 to 40 days after the last dose |
| Visit Day Allowable Window | ±7 | ±7 | ±7 | ±7 | ±7 | +7 | |
| Physical examination | X | X | X | X | X | X | X |
| Vital signs[d] | X | X | X | X | X | X | X |
| Weight | X | X | X | X | X | X | X |
| ECOG performance status | X | X | X | X | X | X | X |
| 12-lead ECG[e] | X | | X | | X | X | X |
| Imaging assessment | X | | | | X | X | |
| Bone density (DXA method) | X | | X | | X | X | |
| Hematology tests | X | X | X | X | X | X | X |
| Blood biochemistry tests | X | X | X | X | X | X | X |
| Blood lipid, sugar, etc. tests | X | X | X | X | X | X | X |
| Urinalysis | X | X | X | X | X | X | X |
| Pharmacodynamic assessments | X | X | X | X | X | X | |
| Tumor marker | X | X | X | X | X | X | |
| QOL assessments | X | X | X | X | X | X | X |
| Concomitant medications/ therapies | Information collected until 30 to 40 days after the last dose | | | | | | |
| Adverse events, etc. | Information collected until 30 to 40 days after the last dose | | | | | | |
| treatment | Oral doses once a day at least 30 minutes before breakfast[f] | | | | | | |

Abbreviations: WK = Week; D = Day; ECOG = Eastern Cooperative Oncology Group; QOL = quality of life; SFU = safety follow-up

a Unless otherwise specified, the assessments will be completed before study drug dosing.
b Additional examinations/assessments may be performed at the discretion of the investigator or sub-investigator.
c If a subject is going to be switched to a GnRH agonist or a GnRH antagonist, this will be done after PK analysis sample collection and assessments have been completed.
d Measurements will be taken after the subject has been sitting down for 5 minutes.
e Measurements will be taken after the subject has been lying down for 5 minutes.
f Study drug will not be taken at WK97D1.

## Appendix D Schedule of Blood Samples Collection for Pharmacokinetic Analysis (Part A)

| Time Point[a] | Dosing Time Point[b] | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D1 | D2 | D3 | D7 | D12 | D13 | D14 | D15 | D21 | D28 | D29 | D30 | D31 | D35 |
| Before dosing[c] | X | X | X | X | X | X | X | X | X | X | X[d] | X[e] | X[f] | X[g] |
| 0.5 hour (± 10 min) postdose | X | | | | | | X | | | | | | | |
| 1 hour (± 15 min) postdose | X | | | | | | X | | | X | | | | |
| 1.5 hours (± 15 min) postdose | X | | | | | | X | | | | | | | |
| 2 hours (± 20 min) postdose | X | | X | X | | | X | | | X | | | | |
| 4 hours (± 20 min) postdose | X | | | | | | X | | | X | | | | |
| 6 hours (± 30 min) postdose | X | | | | | | X | | | | | | | |
| 8 hours (± 30 min) postdose | X | | | | | | X | | | X | | | | |
| 12 hours (± 1 hour) postdose | X | | | | | | X | | | X | | | | |

Abbreviations: D = day

a If a blood sample is going to be collected on an outpatient basis, then the subject will come in for the visit without taking the study drug.
b As a rule, a blood sample will be collected at discontinuation as well, but the blood sample for the post-treatment observation period will not have to be collected.
c Blood samples for PK analysis will be collected within 1 hour before dosing.
d 24 hours (± 1 hour) after dosing on D28
e 48 hours (± 4 hours) after dosing on D28
f 72 hours (± 4 hours) after dosing on D28
g Collected before starting the next treatment

## Appendix E Schedule of Blood Samples Collection for Pharmacokinetic Analysis (Part B)

| Time Point[a] | Dosing Time Point[b] | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | WK1 | | | WK2 | WK3 | WK5 | WK9 | WK13 | WK17 | WK21 | WK25 | WK37 | WK49 |
| | D1[c] | D2 | D4 | D1 | D1 | D1 | D1 | D1 | D1 | D1 | D1 | D1 | D1 |
| Before dosing[d] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 2 hours postdose (± 20 min) | X | | | | | X | | | | | | | |

Abbreviations: WK = week; D = day

a If a blood sample is going to be collected on an outpatient basis, then the subject will come in for the visit without taking the study drug.
b As a rule, blood samples will be collected at discontinuation as well.
c Blood samples will be collected after the subjects have taken the first dose of study drug at the hospital, and then eaten after an interval of at least 30 minutes, and then after another 2 hours have passed.
d Blood samples for PK analysis will be collected within 1 hour before dosing.

## Appendix F Responsibilities of Principal Investigator

1. Conduct the appropriate study in accordance with the protocol and GCP considering the rights, safety and wellbeing of human subjects.
2. When a part of the important activities related to the study are delegated to the sub-investigator or the study support staff, prepare the lists of activities to be delegated and responsible personnel, submit the lists to the head of the site in advance to get them accepted.
3. Prepare a written informed consent form and other written information, and update as appropriate.
4. Confirm the contents of the Clinical Study Agreement.
5. Provide necessary information on the protocol, drugs and responsibilities of individual personnel to the sub-investigator and study support staff, and provide guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide the explanation of the study in writing and obtain the written consent.
7. Assume responsibility for all the medical judgement related to the study.
8. Ensure in collaboration with the head of the site that sufficient information on all clinicaly significant advesrse events related to the study are provided to subjects throughout and beyond the period when subjects participate in the study.
9. If a subject consult other medical institution or other department, notify the physician of the medical institution or department of the subject's participation in the study, as well as the end and termination of the study in writing, and document such records.
10. In case of urgent report of a SAE, immediately notify the head of the site and the sponsor in writing.
11. Prepare correct and complete eCRFs, and submit them to the sponsor with electronic signature.
12. Check and confirm the contents of eCRFs prepared by the sub-investigator or transcribed from the souce data by the study support staff, and submit them to the sponsor with electronic signature.
13. Discuss any proposal from the sponsor including update of the protocol.
14. Notify the head of the site of the end of the study in writing.

## Appendix G ECOG Performance Status

| Score | Activity Level |
|---|---|
| 0 | Normal activity. Fully active, able to carry on all predisease performance without restriction. |
| 1 | Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work). |
| 2 | In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead. |

## Appendix H New York Heart Association (NYHA) Functional Classification

| Class | Patient Symptoms |
|---|---|
| I | Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain. |
| II | Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain. |
| III | Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain. |
| IV | Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased. |

## Appendix I Liver Function Test Abnormality Reporting Checklist

**AS MUCH INFORMATION AS POSSIBLE WILL BE OBTAINED ABOUT THE FOLLOWING PARAMETERS**

**RELATED MEDICAL HISTORY/SYMPTOMS**

☐ Viral hepatitis
☐ Auto-immune disorders
☐ Alcohol use
☐ Biliary disorders
☐ Heart disorders, particularly right heart failure or hypotension
☐ Recent viral diseases
☐ Recent travel
☐ Blood transfusions
☐ Allergies
☐ Recent anesthesia/surgical procedures
☐ Drug abuse
☐ Exposure to toxins
☐ Recent tattoos
☐ Family history of liver disease

**EVENT INFORMATION**

☐ Signs and symptoms

**NOTEWORTHY CLINICAL TEST DATA AND TEST RESULTS**

☐ Hepatic enzymes (ALT, AST, total bilirubin, ALP, GGT)
☐ Coagulation system parameters
☐ Albumin
☐ Virus serum tests
☐ Auto-immune markers
☐ Liver imaging tests (ultrasound, CT, MRI)
☐ Endoscopic retrograde cholangiopancreatography (ERCP)
☐ Liver biopsy
☐ Eosinophil count

## Appendix J Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Incorporating Amendment No.1.

**Page 1, Cover page Sponsor**

**Existing Text**

*Takeda Bio Development Center*

*Marunouchi Eiraku Building*

*1-4-1 Marunouchi, Chiyoda-ku, Tokyo 100-0005*

**Revised Text**

**Takeda Pharmaceutical Company Limited**

**1-1 Doshomachi 4-chome, Chuo-ku, Osaka**

**Rationale for Amendment**

Change in company name and address due to business consolidation.

**Page 1, Cover page CONFIDENTIAL PROPERTY**

**Existing Text**

This document is a confidential communication of *Takeda Bio Development Center*. Acceptance of this document constitutes the agreement by the recipient that no information contained herein will be published or disclosed without written authorization from *Takeda Bio Development Center* except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

**Revised Text**

This document is a confidential communication of **Takeda**. Acceptance of this document constitutes the agreement by the recipient that no information contained herein will be published or disclosed without written authorization from **Takeda** except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

**Rationale for Amendment**

Change in company name due to business consolidation.

**Page 8, Section 2.0 STUDY SUMMARY**

**Existing Text**

**Name of Sponsor:**

*Takeda Bio Development Center*

**Revised Text**

**Name of Sponsor:**

**Takeda Pharmaceutical Company Limited**

**Rationale for Amendment**

Change in company name due to business consolidation.

**Page 31, Section 6.1 Study Design**

**Existing Text**

Cohort/Part Advancement Criteria

•••

In each cohort, if no DLT occurs in even 1 of the 3 subjects during the DLT evaluation period (see Section 6.1.*1*.2), then the dose will be judged tolerable, and the study will proceed to the next cohort.•••

**Revised Text**

**6.1.1** Cohort/Part Advancement Criteria

•••

In each cohort, if no DLT occurs in even 1 of the 3 subjects during the DLT evaluation period (see Section 6.1.**2**.2), then the dose will be judged tolerable, and the study will proceed to the next cohort.•••

**Rationale for Amendment**

Editorial change.

**Page 32 to 33, Section 6.1 Study Design**

**Existing Text**

*6.1.1* DLT

*6.1.1.1* Definition of DLT

•••

*6.1.1.2* DLT Evaluation Period

•••

*6.1.1.3* DLT Evaluable Subjects

•••

**Revised Text**

**6.1.2** DLT

**6.1.2.1** Definition of DLT

•••

**6.1.2.2** DLT Evaluation Period

•••

**6.1.2.3** DLT Evaluable Subjects

•••

**Rationale for Amendment**

Editorial change.

**Page 46, Section 8.1.3 Dose and Regimen**

**Existing Text**

Table 8.b Treatment Groups, Dosages, and Numbers of Tablets (Part B)

| Treatment Group | Dosage/Number of Tablets |
|---|---|
| 80 mg | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 80 mg (Day 2 to Week 48[*3]): Two 40 mg tablets per day |
| 120 mg | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 120 mg (Day 2 to Week 48[*3]): One 80 mg tablet and one 40 mg tablet per day |
| 40 mg[*2] | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 *80 mg* (Day 2 to Week 48[*3]): One 40 mg tablet per day |
| At uptitration | One TAK-385 40 mg tablet per day will be added |

**Revised Text**

Table 8.b Treatment Groups, Dosages, and Numbers of Tablets (Part B)

| Treatment Group | Dosage/Number of Tablets |
|---|---|
| 80 mg | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 80 mg (Day 2 to Week 48[*3]): Two 40 mg tablets per day |
| 120 mg | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 120 mg (Day 2 to Week 48[*3]): One 80 mg tablet and one 40 mg tablet per day |
| 40 mg[*2] | TAK-385 320 mg (Day 1): Four 80 mg tablets per day<br>TAK-385 **40 mg** (Day 2 to Week 48[*3]): One 40 mg tablet per day |
| At uptitration | One TAK-385 40 mg tablet per day will be added |

**Rationale for Amendment**

Correction of typographical error.

**Page 46 to 47, Section 8.1.3.1 Criteria for Upward Dose Adjustments**

**Existing Text**

Part A: The dose of TAK-385 will not be increased even if inadequate testosterone suppression occurs (< 50 ng/dL). If after treatment initiation the serum testosterone level does not drop below 50 ng/dL at 2 or more time points separated by at least 7 days and the investigator determines that the patient needs to be switched to some other treatment, then TAK-385 treatment will be stopped and the patient withdrawn from the study.

Part B: If the following conditions are met, the dose may be adjusted, taking efficacy and safety into consideration. Dose adjustment will be performed when the subject is examined by the investigator.

•••

**Revised Text**

Part A: The dose of TAK-385 will not be increased even if inadequate testosterone suppression occurs (< 50 ng/dL). If after treatment initiation the serum testosterone level does not drop below 50 ng/dL at 2 or more time points separated by at least 7 days and the investigator **or sub-investigator** determines that the patient needs to be switched to some other treatment, then TAK-385 treatment will be stopped and the patient withdrawn from the study.

Part B: If the following conditions are met, the dose may be adjusted, taking efficacy and safety into consideration. Dose adjustment will be performed when the subject is examined by the investigator **or sub-investigator**.

•••

**Rationale for Amendment**

Revised to better fit the actual situation at investigational sites.

**Page 47, Section 8.1.3.2 Criteria for Dose Holds and Dose Reduction**

**Existing Text**

•••

Part B: If a treatment-related AE occurs or if it would be difficult to continue with TAK-385 treatment, then study treatment will be interrupted.•••

**Revised Text**

•••

Part B: If a treatment-related AE occurs or if it would be difficult to continue with TAK-385 treatment, then study treatment will be interrupted **if necessary**.•••

**Rationale for Amendment**

Revised for consistency with text regarding Part A.

## Page 48, Section 8.1.3.2 Criteria for Dose Holds and Dose Reduction

### Existing Text

Table 8.c Guidelines for Handling Liver Function Test Abnormalities

| Category | ALT, AST, and Total Bilirubin | Study Drug | ALT and AST Tests | Treatment Interruption | Dose Adjustment |
|---|---|---|---|---|---|
| A | ALT or AST ≥ 1.5 × ULN to < 3 × ULN<br>AND<br>Total bilirubin < 1.5 × ULN | Continue without changing the dose | Perform tests every week for 2 weeks, and then every 2 weeks for 4 weeks until stable[*1] | Not necessary | Not necessary |
| B | ALT or AST ≥ 3 × ULN to < 5 × ULN<br>AND<br>Total bilirubin < 1.5 × ULN | Continue without changing the dose | Perform tests every week *for 2 weeks*, and then every 2 weeks for 4 weeks until stable[*1] | Not necessary | Not necessary |
| C | ALT or AST ≥ 5 × ULN to < 8 × ULN<br>AND<br>Total bilirubin < 1.5 × ULN | Interrupt treatment | Perform 2 tests in the first week, then every week for 2 weeks, and then every 2 weeks until stable[*1] | Interrupt treatment until stable[*1] | Reduce the TAK-385 dose to 40 mg |
| D | ALT or AST *> 8 × ULN* to < 20 × ULN<br>AND<br>Total bilirubin < 1.5 × ULN | Interrupt treatment | Perform 2 tests a week for the first 2 weeks, and then every 2 weeks until stable[*1] | Interrupt treatment until stable[*1] | Reduce the TAK-385 dose to 40 mg[*2] |
| E | ALT or AST ≥ 3× ULN<br>AND<br>Total bilirubin > 2 × ULN<br>(Hy's law) | Permanently discontinue treatment | Perform 2 tests a week until the test values drop, and then every week until stable[*1] | N/A | N/A |

## Revised Text

Table 8.c Guidelines for Handling Liver Function Test Abnormalities

| Category | ALT, AST, and Total Bilirubin | Study Drug | ALT and AST Tests | Treatment Interruption | Dose Adjustment |
|---|---|---|---|---|---|
| A | ALT or AST ≥ 1.5 × ULN to < 3 × ULN<br>AND<br>Total bilirubin < 1.5 × ULN | Continue without changing the dose | Perform tests every week for 2 weeks, and then every 2 weeks for 4 weeks until stable[*1] | Not necessary | Not necessary |
| B | ALT or AST ≥ 3 × ULN to < 5 × ULN<br>AND<br>Total bilirubin < 1.5 × ULN | Continue without changing the dose | Perform tests every week, and then every 2 weeks for 4 weeks until stable[*1] | Not necessary | Not necessary |
| C | ALT or AST ≥ 5 × ULN to < 8 × ULN<br>AND<br>Total bilirubin < 1.5 × ULN | Interrupt treatment | Perform 2 tests in the first week, then every week for 2 weeks, and then every 2 weeks until stable[*1] | Interrupt treatment until stable[*1] | Reduce the TAK-385 dose to 40 mg |
| D | ALT or AST **≥ 8 × ULN** to < 20 × ULN<br>AND<br>Total bilirubin < 1.5 × ULN | Interrupt treatment | Perform 2 tests a week for the first 2 weeks, and then every 2 weeks until stable[*1] | Interrupt treatment until stable[*1] | Reduce the TAK-385 dose to 40 mg[*2] |
| E | ALT or AST ≥ 3× ULN<br>AND<br>Total bilirubin > 2 × ULN<br>(Hy's law) | Permanently discontinue treatment | Perform 2 tests a week until the test values drop, and then every week until stable[*1] | N/A | N/A |

## Rationale for Amendment

Correction of typographical error.

## Page 52, Section 9.1.8 Clinical Laboratory Tests

### Existing Text

Table 9.a Clinical Laboratory Tests

| Hematology | Chemistry | Metabolic Panel | Urinalysis |
|---|---|---|---|
| RBC | Total protein | Triglycerides | pH |
| WBC | Albumin | Total cholesterol | Specific gravity |
| Hemoglobin | Glucose | HDL cholesterol | Protein (qualitative) |
| Hematocrit | Creatinine | LDL cholesterol | Glucose (qualitative) |
| Platelet count | BUN | TSH | Occult blood (qualitative) |
| Differential WBC (neutrophils [including absolute count], basophils, eosinophils, lymphocytes, monocytes) | Uric acid | HbA1c | Ketones (qualitative) |
| | Total bilirubin | | Urobilinogen (qualitative) |
| | ALT | | Bilirubin (qualitative) |
| | AST | | |
| | LDH | | |
| | γ-GTP | | |
| | ALP | | |
| | CK (CPK) | | |
| | Na | | |
| | K | | |
| | Cl | | |
| | Ca | | |
| | P | | |
| | PT-INR | | |
| **Tests to be conducted when determining eligibility** | | | |
| (to be performed only when deemed necessary) | | | |
| HIV test, hepatititis tests including HBsAg and anti-HCV | | | |

**Revised Text**

Table 9.a Clinical Laboratory Tests

| Hematology | Chemistry | Metabolic Panel | Urinalysis |
|---|---|---|---|
| RBC | Total protein | Triglycerides | pH |
| WBC | Albumin | Total cholesterol | Specific gravity |
| Hemoglobin | Glucose | HDL cholesterol | Protein (qualitative) |
| Hematocrit | Creatinine | LDL cholesterol | Glucose (qualitative) |
| Platelet count | BUN | TSH | Occult blood (qualitative) |
| Differential WBC (neutrophils [including absolute count], basophils, eosinophils, lymphocytes, monocytes) | Uric acid | HbA1c | Ketones (qualitative) |
| | Total bilirubin | | Urobilinogen (qualitative) |
| | ALT | | Bilirubin (qualitative) |
| | AST | | |
| | LDH | | |
| | γ-GTP | | |
| | ALP | | |
| | CK (CPK) | | |
| | Na | | |
| | K | | |
| | Cl | | |
| | Ca | | |
| | P | | |
| | PT-INR | | |
| **Tests to be conducted when determining eligibility** | | | |
| (to be performed only when deemed necessary) | | | |
| HIV test**;** hepatititis tests including HBsAg and anti-HCV**; serologic test for syphilis** | | | |

**Rationale for Amendment**

Editorial change.

**Page 57, Section 9.3.1 Screening**

**Existing Text**

•••

- 12-lead ECG
- Imaging assessments

•••

**Revised Text**

•••

- 12-lead ECG

- **Chest X-ray examination**
- Imaging assessments

•••

**Rationale for Amendment**

Editorial change.

**Page 58, Section 9.3.3 Day of Study Treatment Initiation**

**Existing Text**

The following tests, observations, and assessments will be performed before study drug is administered on the day of study treatment initiation. If clinical laboratory tests were performed at screening up to 3 days prior to treatment initiation, then they may be used as the tests performed prior to treatment initiation.

•••

**Revised Text**

The following tests, observations, and assessments will be performed before study drug is administered on the day of study treatment initiation. If **12-lead ECG or** clinical laboratory tests were performed at screening up to 3 days prior to treatment initiation, then they may be used as the tests performed prior to treatment initiation.

•••

**Rationale for Amendment**

Revised to better fit the actual situation at investigational sites.

**Page 66, Section 10.1.3 Additional Points to Consider for Pretreatment Events and Adverse Events**

**Existing Text**

•••

*Changes in severity of AEs/serious PTEs:*
*If the subject experiences changes in severity of an AE/serious PTE, the event sould be captured once withmaximum severity recorded.*

Underlying disease:

•••

**Revised Text**

•••

Underlying disease:

•••

**Rationale for Amendment**

Deleted due to inconsistency with the conditions stipulated in Section 10.1.6.

**Page 73, Section 10.2.1.3 Reporting of Special Interest Adverse Events**

**Existing Text**

•••The principal investigator will also prepare a report of LFT abnormalities (same report form as for SAEs) within 10 business days, and submit it with a signature or printed name and personal seal to the contact identified in the attachment. The " Liver Function Test Abnormality Reporting Checklist (Appendix I)" will be used as reference to assist in the preparation of the report.

•••

**Revised Text**

•••The principal investigator will also prepare a report of LFT abnormalities (same report form as for SAEs) within 10 business days, and submit it with a signature or printed name and personal seal to the contact identified in the attachment. The "Liver Function Test Abnormality Reporting Checklist (Appendix I)" will be used as reference to assist in the preparation of the report.

•••

**Rationale for Amendment**

Correction of typographical error. (Note: Does not apply to English protocol.)

**Page 74, Section 10.2.2 Collection and Reporting of Serious Adverse Events**

**Existing Text**

•••

After the initial report of the SAE, the principal investigator will *immediately* report detailed information to the sponsor.•••

**Revised Text**

•••

After the initial report of the SAE, the principal investigator will report detailed information to the sponsor **within 10 calendar days**.•••

**Rationale for Amendment**

Clarification of the due date for reporting.

**Page 79, Section 13.1.1 Analysis Sets**

**Existing Text**

•••The DLT analysis set will be defined as all subjects who can be evaluated for DLTs (see Section 6.1.*1*.3). The analysis sets will be defined in detail in the separately prepared "Rules for Handling Analytical Data."

**Revised Text**

•••The DLT analysis set will be defined as all subjects who can be evaluated for DLTs (see Section 6.1.**2**.3). The analysis sets will be defined in detail in the separately prepared "Rules for Handling Analytical Data."

**Rationale for Amendment**

Editorial change.

**Page 79, Section 13.1.3 Efficacy Analysis**

**Existing Text**

1) PSA

•••Waterfall plots of the change from baseline at *the Week 12 dose* (LOCF) and the change from baseline for the minimum value after the start of study drug treatment will be prepared by dose.

**Revised Text**

1) PSA

•••Waterfall plots of the change from baseline at **Week 13 Day 1** (LOCF) and the change from baseline for the minimum value after the start of study drug treatment will be prepared by dose.

**Rationale for Amendment**

Editorial change.

## Page 90 to 91, Appendix A Schedule of Study Procedures (Part A)

### Existing Text

| Procedure[a] | Subject consent[b] | Screening | Treatment Period[c] | | | | | | | | | | SFU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Inpatient[f] | | | | | | | | Outpatient | | |
| | | Before treatment initiation D -28 to D -1[g] | D1[h] | D2 | D3 | D7 | D12 | D13 | D14 | D15 | D21 | D28 | 30 to 40 days after the last dose |
| Allowable visit window | | | 0 | | | | | | | | ±1 | 0 | |
| Confirmation of eligibility | | X | | | | | | | | | | | |
| Subject background[l] | | X | | | | | | | | | | | |
| Physical examination | | X | X | X | X | X | | | X | | X | X | X |
| Vital signs[k] | | X | X | | | X | | | X | | X | X | X |
| Weight/height[l] | | X | X | | | X | | | X | | X | X | X |
| ECOG performance status | | X | | | | | | | | | | X | X |
| 12-lead ECG[m] | | X | X | | | | | | X | | | X | X |
| Imaging assessment[n] | | X | Measure as appropriate | | | | | | | | | | |
| Hematology tests | | X | X[o] | | | X | | | X | | X | X | X |
| Blood biochemistry tests | | X | X[o] | | | X | | | X | | X | X | X |
| Blood lipid, sugar, etc. tests | | X | X[o] | | | | | | | | | X | X |
| Urinalysis | | X | X | | | X | | | X | | X | X | X |
| Heart-related tests | | X | Measure as appropriate | | | | | | | | | | |
| Pharmacodynamic assessments | | X | | X | X | X | | | X | | X | X | |
| Tumor marker | | X | | | | | | | | | | X | |
| Pharmacokinetic assessments[p] | | | X | X | X | X | X | X | X | X | X | X | |
| PGx sample collection | | | X (during the treatment period) | | | | | | | | | | |
| Concomitant medications/ therapies | | Collected from the time of informed consent until 30 to 40 days after the last dose | | | | | | | | | | | |
| Adverse events, etc. | | PTEs[r] | Information collected from study treatment initiation until 30 to 40 days after the last dose | | | | | | | | | | |
| Study treatment | | | Oral doses once a day at least 30 minutes before breakfast | | | | | | | | | | |

Abbreviations: D = Day; ECOG = Eastern Cooperative Oncology Group; PGx = pharmacogenomics*; PSA = prostate-specific antigen*; SFU = safety follow-up

•••

c Additional examinations/assessments may be performed at the discretion of the investigator.

•••

f Day 1: Day of treatment initiation. As a rule, subjects will not be allowed to leave the investigational site or return home during the inpatient period. *However, if this is unavoidable, then it may be allowed, at the discretion of the investigator.*

•••

## Revised Text

Appendix A Schedule of Study Procedures (Part A)

| Procedure[a] | Subject consent[b] | Screening | Treatment Period[c] | | | | | | | | | | SFU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Inpatient[f] | | | | | | | | Outpatient | | |
| | | Before treatment initiation D -28 to D -1[g] | D1[h] | D2 | D3 | D7 | D12 | D13 | D14 | D15 | D21 | D28 | 30 to 40 days after the last dose |
| Allowable visit window | | | 0 | | | | | | | | ±1 | 0 | |
| Confirmation of eligibility | | X | | | | | | | | | | | |
| Subject background[l] | | X | | | | | | | | | | | |
| Physical examination | | X | X | X | X | X | | | X | | X | X | X |
| Vital signs[k] | | X | X | | | X | | | X | | X | X | X |
| Weight/height[l] | | X | X | | | X | | | X | | X | X | X |
| ECOG performance status | | X | | | | | | | | | | X | X |
| 12-lead ECG[m] | | X | **X[o]** | | | | | | X | | | X | X |
| **Chest X-ray examination** | | **X** | | | | | | | | | | | |
| Imaging assessment[n] | | X | Measure as appropriate | | | | | | | | | | |
| Hematology tests | | X | X[o] | | | X | | | X | | X | X | X |
| Blood biochemistry tests | | X | X[o] | | | X | | | X | | X | X | X |
| Blood lipid, sugar, etc. tests | | X | X[o] | | | | | | | | | X | X |
| Urinalysis | | X | **X[o]** | | | X | | | X | | X | X | X |
| Heart-related tests | | X | Measure as appropriate | | | | | | | | | | |
| Pharmacodynamic assessments | | X | | X | X | X | | | X | | X | X | |
| Tumor marker | | X | | | | | | | | | | X | |
| Pharmacokinetic assessments[p] | | | X | X | X | X | X | X | X | X | X | X | |
| PGx sample collection | | | X (during the treatment period) | | | | | | | | | | |
| Concomitant medications/ therapies | | Collected from the time of informed consent until 30 to 40 days after the last dose | | | | | | | | | | | |
| Adverse events, etc. | | PTEs[r] | Information collected from study treatment initiation until 30 to 40 days after the last dose | | | | | | | | | | |
| Study treatment | | | Oral doses once a day at least 30 minutes before breakfast | | | | | | | | | | |

Abbreviations: D = Day; ECOG = Eastern Cooperative Oncology Group; PGx = pharmacogenomics; SFU = safety follow-up

•••

c Additional examinations/assessments may be performed at the discretion of the investigator **or sub-investigator.**

•••

f Day 1: Day of treatment initiation. As a rule, subjects will not be allowed to leave the investigational site or return home during the inpatient period. **However, the investigator or sub-investigator may allow the subject to return home temporarily.**

•••

## Rationale for Amendment

Editorial change, and revision for consistency with description in Section 7.4.

## Page 92 to 93, Appendix B Schedule of Study Procedures (Part B – Screening to Week 48, SFU)

### Existing Text

| Procedure[a] | Informed consent[b] | Screening | Treatment Period[cd] | | | | | | | | SFU |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Day | | Before treatment initiation[e] D -28 to D -1[f] | WK 1 D1[h] | WK 1 D2 | WK 1 D4 | WK 2 D1 | WK 3 D1 | WK 5 D1 | WK 9 D1 | WK 13 D1 | 30 to 40 days after the last dose |
| Allowable visit window | | | 0 | 0 | 0 | ±1 | ±1 | ±2 | ±2 | ±2 | |
| Confirmation of eligibility | | X | | | | | | | | | |
| Subject background[i] | | X | | | | | | | | | |
| Physical examination | | X | X | X | X | X | X | X | X | X | X |
| Vital signs[j] | | X | X | | | X | X | X | X | X | X |
| Weight/height[k] | | X | X | | | X | X | X | X | X | X |
| ECOG performance status | | X | | | | | | X | | | X |
| 12-lead ECG[l] | | X | *X* | | | | X | X | | | X |
| Ophthalmology tests | | X | | | | | | | | | |
| Imaging assessment | | X | | | | | | | | | |
| Bone density (DXA method) | | X | | | | | | | | | |
| Hematology tests | | *X*[m] | *X*[m] | | | | | X | X | X | X |
| Blood biochemistry tests | | *X*[m] | *X*[m] | | | | | X | X | X | X |
| Blood lipid, sugar, etc. tests | | *X*[m] | *X*[m] | | | | | X | X | X | X |
| Urinalysis | | X | *X* | | | | | X | X | X | X |
| Heart-related tests | | X | Measure as appropriate | | | | | | | | |
| Pharmacodynamic assessments | | X | *X*[n] | X | X | *X*[n] | *X*[n] | *X*[n] | *X*[n] | *X*[n] | |
| Tumor marker | | X | | | | | | X | X | X | |
| BMP concentration[o] | | | X | | | | | | X | | |
| Pharmacokinetic assessments[p] | | | X | X | X | X | X | X | X | X | |
| PGx sample collection | | X (randomization through the treatment period) | | | | | | | | | |
| QOL assessments | | X | X | | | | | X | X | X | X |
| Concomitant medications/ therapies | | Collected from the time of informed consent until 30 to 40 days after the last dose | | | | | | | | | |
| Adverse events, etc. | | PTEs[r] | Information collected from study treatment initiation until 30 to 40 days after the last dose | | | | | | | | |
| treatment | | | Oral doses once a day at least 30 minutes before breakfast | | | | | | | | |

Abbreviations: WK = Week; D = Day; ECOG = Eastern Cooperative Oncology Group; PGx = pharmacogenomics; QOL = quality of life; SFU = safety follow-up

•••

c Additional examinations/assessments may be performed at the discretion of the investigator.

•••

l 12-lead ECG measurements will be taken after the subject has been lying down for at least 5 minutes.

*m* Results of tests performed up to 3 days before treatment initiation may be used at the D1 test results.

*n* Blood samples will also be collected for the serum testosterone high-sensitivity measurements. However, at *W1D1*, only the high-sensitivity measurements will be performed.

*o* Blood and urine sample collection

*p* See Appendix E for detailed sample collection times

*q* As a rule, blood samples will also be collected at withdrawal from the study.

*r* Information will be collected from consent acquisition until treatment initiation.

## Revised Text (Note: Footnote number carried down in the same manner in the area of the table not displayed below)

| Procedure[a] | | Screening | Treatment Period[cd] | | | | | | | | SFU |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Day | | Before treatment initiation[e] D -28 to D -1[f] | WK 1 D1[h] | WK 1 D2 | WK 1 D4 | WK 2 D1 | WK 3 D1 | WK 5 D1 | WK 9 D1 | WK 13 D1 | 30 to 40 days after the last dose |
| Allowable visit window | | | 0 | 0 | 0 | ±1 | ±1 | ±2 | ±2 | ±2 | |
| Confirmation of eligibility | | X | | | | | | | | | |
| Subject background[l] | | X | | | | | | | | | |
| Physical examination | | X | X | X | X | X | X | X | X | X | X |
| Vital signs[j] | | X | X | | | X | X | X | X | X | X |
| Weight/height[k] | | X | X | | | X | X | X | X | X | X |
| ECOG performance status | | X | | | | | | X | | | X |
| 12-lead ECG[l] | | X | **X[n]** | | | | X | X | | | X |
| **Chest X-ray examination** | | **X** | | | | | | | | | |
| Ophthalmology tests | Informed consent[b] | X | | | | | | | | | |
| Imaging assessment[m] | | X | | | | | | | | | |
| Bone density (DXA method) | | X | | | | | | | | | |
| Hematology tests | | **X** | **X[n]** | | | | | X | X | X | X |
| Blood biochemistry tests | | **X** | **X[n]** | | | | | X | X | X | X |
| Blood lipid, sugar, etc. tests | | **X** | **X[n]** | | | | | X | X | X | X |
| Urinalysis | | X | **X[n]** | | | | | X | X | X | X |
| Heart-related tests | | X | Measure as appropriate | | | | | | | | |
| Pharmacodynamic assessments | | X | **X[o]** | X | X | **X[o]** | **X[o]** | **X[o]** | **X[o]** | **X[o]** | |
| Tumor marker | | X | | | | | | X | X | X | |
| BMP concentration[p] | | | X | | | | | | X | | |
| Pharmacokinetic assessments[q] | | | X | X | X | X | X | X | X | X | |
| PGx sample collection | | | X (randomization through the treatment period) | | | | | | | | |
| QOL assessments | | X | X | | | | | X | X | X | X |
| Concomitant medications/ therapies | | Collected from the time of informed consent until 30 to 40 days after the last dose | | | | | | | | | |
| Adverse events, etc. | | PTEs[s] | Information collected from study treatment initiation until 30 to 40 days after the last dose | | | | | | | | |
| treatment | | | Oral doses once a day at least 30 minutes before breakfast | | | | | | | | |

Abbreviations: WK = Week; D = Day; ECOG = Eastern Cooperative Oncology Group; PGx = pharmacogenomics; QOL = quality of life; SFU = safety follow-up

•••

c Additional examinations/assessments may be performed at the discretion of the investigator **or sub-investigator**.

•••

l 12-lead ECG measurements will be taken after the subject has been lying down for at least 5 minutes.

**m Performed at screening only if imaging assessments were not performed within 28 days prior to treatment initiation, or if no usable images are available for the subject.**

**n** Results of tests performed up to 3 days before treatment initiation may be used as the D1 test results.

**o** Blood samples will also be collected for the serum testosterone high sensitivity measurements. However, at **WK1D1**, only the high-sensitivity measurements will be performed.

**p** Blood and urine sample collection
**q** See Appendix E for detailed sample collection times
**r** As a rule, blood samples will also be collected at withdrawal from the study.
**s** Information will be collected from consent acquisition until treatment initiation.

### Rationale for Amendment

Editorial change, and revision to better fit the actual situation at investigational sites.

## Page 94, Appendix C Schedule of Study Procedures (Part B – Weeks 49 to 96)

### Existing Text

Abbreviations: WK = Week; D = Day; ECOG = Eastern Cooperative Oncology Group; QOL = quality of life; SFU = safety follow-up
•••
b Additional examinations/assessments may be performed at the discretion of the investigator.
•••

### Revised Text

Abbreviations: WK = Week; D = Day; ECOG = Eastern Cooperative Oncology Group; QOL = quality of life; SFU = safety follow-up
•••
b Additional examinations/assessments may be performed at the discretion of the investigator **or sub-investigator.**
•••

### Rationale for Amendment

Correction of typographical error (Note: Does not apply to English protocol.), and revision to better fit the actual situation at investigational sites.

## Page 95, Appendix D Schedule of Blood Samples Collection for Pharmacokinetic Analysis (Part A)

### Existing Text

Abbreviations: *WK = week;* D = day
•••
c Blood samples for PK analysis will be collected within 1 hour before dosing.
•••

### Revised Text

Abbreviations: D = day
•••
c Blood samples for PK analysis will be collected within 1 hour before dosing.
•••

### Rationale for Amendment

Editorial change.

**Page 96, Appendix E Schedule of Blood Samples Collection for Pharmacokinetic Analysis (Part B)**

**Existing Text**

| Time Point[a] | Dosing Time Point[b] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | WK1 | | | WK2 | WK 3 | WK 5 | WK 25 | WK 37 | WK 49 |
| | D1[c] | D2 | D4 | D1 | D1 | D1 | D1 | D1 | D1 |
| Before dosing[d] | X | X | X | X | X | X | X | X | X |
| 2 hours postdose | X | | | | | X | | | |

Abbreviations: WK = week; D = day

•••

**Revised Text**

| Time Point[a] | Dosing Time Point[b] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | WK1 | | | WK2 | WK3 | WK5 | WK25 | WK37 | WK49 |
| | D1[c] | D2 | D4 | D1 | D1 | D1 | D1 | D1 | D1 |
| Before dosing[d] | X | X | X | X | X | X | X | X | X |
| 2 hours postdose **(± 20 min)** | X | | | | | X | | | |

Abbreviations: WK = week; D = day

•••

**Rationale for Amendment**

Editorial change.

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

## ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy HH:mm 'UTC') |
|---|---|---|
| [redacted] | Clinical Approval | 26-Sep-2017 01:43 UTC |