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).

PROTOCOL

<Title>

A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Oral TAK-385 40 mg in the Treatment of Pain Symptoms associated with Uterine Fibroids

<Short Title>

A Placebo-Controlled, Phase 3 Study of TAK-385 40 mg in the Treatment of Pain Symptoms associated with Uterine Fibroids

Sponsor:	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome, Chuo-ku, Osaka		
Study Identifier:	TAK-385-3008		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	TAK-385		
Date:	3 December 2015		

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

See the attachment 1.

1.2 Principles of Clinical Studies

This study will be conducted with the highest respect for the individual participants in accordance with the 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.

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2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Clinical Study Sponsor:
Takeda Pharmaceutical Company Limited</td><td>Compound:
TAK-385</td></tr>
<tr><td>Study Title: A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Oral TAK-385 40 mg in the Treatment of Pain Symptoms associated with Uterine Fibroids</td><td>IND No.:
Not Applicable</td><td>EudraCT No.:
Not Applicable</td></tr>
<tr><td colspan="2">Study Identifier: TAK-385-3008</td><td>Phase: 3</td></tr>
<tr><td colspan="3">Study Design:
This is a phase 3, multicenter, randomized, double-blind, parallel-group study to evaluate the efficacy of TAK-385 40 mg administered orally once daily for 12 weeks compared with placebo in subjects having pain symptoms associated with uterine fibroids.
Subjects must be diagnosed to have uterine fibroids confirmed by transvaginal ultrasound or other methods. Subjects must experience pain symptoms associated with uterine fibroids (eg, lower abdominal pain and low back pain). The total number of subjects to be randomized under double-blind conditions is 64 (32 subjects each for the TAK-385 40 mg group or placebo group).
After signing the informed consent form, subjects will start recording in the patient diary from the day of VISIT 1. During the period between VISIT 2 and VISIT 3, in which subjects must experience 1 menstrual cycle, the baseline values for the efficacy evaluation of pain symptoms will be collected. Subjects should record in the patient diary every day until the end of study drug administration. VISIT 2 should be between the first and fifth day of the first menstruation after VISIT 1. The study drug (TAK-385 placebo) will be administered under single-blind conditions from the day of first menstruation after VISIT 1 to the day before VISIT 3. VISIT 3 should be between the first and fifth day of the second menstruation after VISIT 1. From VISIT 2 to 6, subjects should try to visit the study site during the morning in a fasted state and before taking the study drug. Subjects will be randomized in a 1:1 ratio to either TAK-385 40 mg group or placebo group at VISIT 3. Study drug (TAK-385 40 mg or TAK-385 placebo) will be administered from the day of VISIT 3 to the day before VISIT 6 (or until early termination) under double-blind conditions.
This study consists of Screening of approximately 1 to 6 weeks, a Run-in period of 3 to 6 weeks, a Treatment period of 12 weeks, and a Follow-up period of 4 weeks. The total period of study participation is approximately 20 to 28 weeks. If the recovery of the first post-treatment menstruation is not observed by the visit at the end of the Follow-up (VISIT 7), the subject will undergo further follow-up using possible means such as by telephone interview, until the recovery of the first post-treatment menstruation is observed. During the course of this study, subjects will visit the study site to undergo the designated examinations and evaluations at each visit.</td></tr>
<tr><td colspan="3">Primary Objective:
The primary objective of this study is to evaluate the efficacy of TAK-385 40 mg administered orally once daily for 12 weeks, compared with placebo in subjects having pain symptoms associated with uterine fibroids.</td></tr>
<tr><td colspan="3">Secondary Objective:
The secondary objective of this study is to evaluate the safety of TAK-385 40 mg administered orally once daily for 12 weeks, compared with placebo in subjects having pain symptoms associated with uterine fibroids.</td></tr>
<tr><td colspan="3">Subject Population: Subjects aged 20 years or older inclusive, with uterine fibroids</td></tr>
<tr><td colspan="2">Planned Number of Subjects:
The following number of subjects will be randomized:
TAK-385 40 mg group : 32 subjects
Placebo group : 32 subjects
Total : 64 subjects</td><td>Planned Number of Sites:
Approximately 15 sites</td></tr>
</table>

Dose Levels:	**Route of Administration:**
TAK-385 Dose: 40 mg or placebo Regimen: Administered once daily before breakfast	Oral
Duration of Treatment:	**Study Length:**
12 weeks	Screening, Run-in, Treatment (12 weeks), Follow-up (4 weeks)

Inclusion Criteria:

Subject eligibility is determined according to the following criteria prior to entry into the study:

Inclusion Criteria for Entering the Screening (at VISIT 1)

1. In the opinion of the investigator or subinvestigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form prior to the initiation of any study procedures.
3. Prior to VISIT 1, the subject has a diagnosis of uterine fibroids confirmed by transvaginal ultrasound, abdominal ultrasound, magnetic resonance imaging (MRI), computed tomography (CT), or laparoscopy, and has never received surgical treatment for the myoma (measurable noncalcified myoma with a longest diameter of ≥3 cm).
4. The subject is a premenopausal Japanese woman.
5. The subject is aged 20 years or older on the day of signing and dating the informed consent form.
6. The subject has 1 or more measurable noncalcified myomas with a longest diameter of ≥3 cm confirmed by transvaginal ultrasound.
7. The subject has experienced 1 or more regular menstrual cycles (25 to 38 days) immediately prior to VISIT 1 and that should include menstrual bleeding of at least 3 consecutive days.
8. The subject who is sexually active with a nonsterilized male partner agrees to use routinely adequate contraception from signing of informed consent throughout the duration of the study.

Inclusion Criteria for Entering the Run-in (at VISIT 2)

9. The subject has experienced regular menstrual cycles (25 to 38 days) immediately prior to VISIT 2 that should include menstrual bleeding of at least 3 consecutive days (at least 2 regular menstruation cycles to be confirmed by Inclusion criteria #7 and #9).

Inclusion Criteria for Entering the Treatment (at VISIT 3)

10. The subject has 1 or more measurable noncalcified myomas, with a longest diameter of ≥3 cm confirmed by transvaginal ultrasound (the same myoma should be measured as in Inclusion criterion #6).
11. The subject has a maximum Numerical Rating Scale (NRS) score of ≥4 in 1 menstrual cycle just before VISIT 3.
12. The subject has pain symptoms associated with uterine fibroids of at least 2 days in 1 menstrual cycle just before VISIT 3.
13. The subject has experienced regular menstrual cycles (25 to 38 days) after VISIT 1 that should include menstrual bleeding of at least 3 consecutive days (at least 3 regular menstruation cycles to be confirmed by Inclusion criteria #7, #9 and #13).

Exclusion Criteria:

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received any investigational compound within 24 weeks prior to the start of the administration of the study medication for the day of first menstruation after VISIT 1.
2. The subject has received TAK-385 (including placebo) in a previous clinical study.
3. The subject is an immediate family member, study site employee, or is in a dependant relationship with a study

site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

4. The subject has lower abdominal pain due to irritable bowel syndrome or severe interstitial cystitis.
5. The subject has a current history of thyroid gland disorder with irregular menstruation, or has a potential for irregular menstruation due to thyroid gland disorder, as determined by the investigator or subinvestigator.
6. The subject has a previous or current history of pelvic inflammatory disease within the 8 weeks prior to VISIT 1.
7. The subject has a positive Pap smear test result conducted within the 1 year prior to VISIT 1 (if there are no previous test results, those who were judged positive in the test conducted before VISIT 2).
8. The subject has a history of panhysterectomy or bilateral oophorectomy.
9. The subject has had markedly abnormal uterine bleeding or anovulatory bleeding, as determined by the investigator or subinvestigator.
10. The subject has a malignant tumor or a history of a malignant tumor within the 5 years prior to VISIT 1.
11. The subject has been treated with selective estrogen receptor modulators (SERMs) (excluding drugs for external use and dietary supplements) within the 4 weeks prior to VISIT 2.
12. The subject has been treated with any of the following drugs within the 8 weeks prior to VISIT 2: oral contraceptive or sex hormone preparations (norethindrone, norethisterone, medroxyprogesterone, estrogen, or other progestins), and within the 16 weeks prior to VISIT 2: gonadotropin-releasing hormone (GnRH) analogues, dienogest, danazol, or aromatase inhibitors (for 1- and 3-month sustained-release preparations, within the 20 and 28 weeks prior to VISIT 2, respectively).
13. The subject has a previous or current history of severe hypersensitivity or severe allergies to drugs.
14. The subject has nondiagnosable abnormal genital bleeding.
15. Female subject who is pregnant, lactating, or intending to become pregnant or to donate ova prior to signing of informed consent, during the study period, or within 1 month after the end of the study.
16. The subject has clinically significant cardiovascular disease (eg, myocardial infarction or unstable angina pectoris within the 24 weeks prior to VISIT 1) or uncontrollable hypertension (eg, resting systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg at Screening and Run-in).
17. The subject is inappropriate for participation in this study based on standard 12-lead electrocardiogram (ECG) findings, as determined by the investigator or subinvestigator.
18. The subject has active liver disease or jaundice, or with alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin (total bilirubin) >1.5 times the upper limit of normal (ULN) in the clinical laboratory tests at VISIT 1 and 2.
19. The subject has previous or current history of diseases considered to be inappropriate for participation in this study, including severe hepatic impairment, jaundice, renal impairment, cardiovascular disease, endocrine system disease, metabolic disorder, pulmonary disease, gastrointestinal disease, neural disease, urological disease, immune disease, or mental disorder (especially depression-like symptoms) or suicide attempt resulting from a mental disorder.
20. The subject has a previous or current history of drug abuse (defined as any illicit drug use) or alcohol abuse.
21. The subject is inappropriate for participation in this study for other reasons, as determined by the investigator or subinvestigator.

Main Criteria for Evaluation and Analyses:

Primary Endpoint

1) Efficacy:

Proportion of subjects with a maximum NRS score of 1 or less during the 28 days before the final dose of study drug

Secondary Endpoints

1) Efficacy:

- Proportion of subjects with a maximum NRS score of 0 during the 28 days before the final dose of study drug
- Mean NRS score during the 28 days before the final dose of study drug
- Number of days without pain symptoms (NRS = 0) during the 28 days before the final dose of study drug

2) Safety:

- Adverse events (AEs), vital signs, weight, standard 12-lead ECG, clinical laboratory tests

Additional Endpoints

- Proportion of days using analgesics during the 28 days before the final dose of study drug
- Luteinizing hormone (LH), follicle-stimulation hormone (FSH), estradiol (E_2), and progesterone (P) (Week 4, 8, 12 and Follow-up)

Statistical Considerations:

Primary analysis

The following analyses will be performed based on the full analysis set (FAS):

The proportion of subjects with a maximum NRS score of 1 or less during the 28 days before the final dose of study drug will be summarized by treatment group. Comparison between the treatment groups will be performed using Fisher's exact test.

Secondary analysis

An analysis similar to the above “Primary analysis” will be performed using the per protocol set (PPS) to assess the robustness of the results (sensitivity analysis).

Sample Size Justification:

Within the subjects who recorded maximum NRS score of ≥4 during 1 menstrual cycle just before the start of the Treatment drug administration in the TAK-385 phase 2 study in Japanese patients with uterine fibroids, the proportion of subjects with a maximum NRS score of 1 or less during the 28 days before the final dose of study drug was 14.7% (5/34) in placebo group and 75.9% (22/29) in TAK-385 40 mg group.

A sample size of 28 per group would give a power of >90% when a Fisher’s exact test with a significance level of 5% (2-sided) is used for the comparison between TAK-385 40 mg group and placebo group, under the assumption that “the proportion of subjects with a maximum NRS score of 1 or less during the 28 days before the final dose of study drug” is 20.0% for placebo group and 65.0% for TAK-385 40 mg group (SAS ver.9.2 Power procedure).

Based on the above, 28 subjects are considered sufficient for the number of evaluable subjects per group. Thirty two subjects are to be randomized to each group on the assumption that some subjects will be excluded from the analysis of the primary endpoint.

3.0 LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the blood concentration-time curve
BMD	bone mineral density
BMI	body mass index
BUN	blood urea nitrogen
C_{max}	maximum observed plasma concentration
CRF	case report form
CRO	contract research organization
CT	computed tomography
E_2	estradiol
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDA	Food and Drug Administration
Fe	iron
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GnRH	gonadotropin-releasing hormone
HGB	hemoglobin
HDL	high density lipoprotein
hCG	human chorionic gonadotropin
HCT	hematocrit
ICH	International Conference on Harmonisation
INN	international non-proprietary name
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LFT	liver function test
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
NILM	negative for intraepithelial lesion or malignancy

NRS	numerical rating scale
NSAIDs	non-steroidal anti-inflammatory drugs
P	progesterone
PBAC	pictorial blood loss assessment chart
P-gp	P-glycoprotein
PGx	pharmacogenomics
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	per protocol set
PT	preferred term
QOL	quality of life
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SERM	selective estrogen receptor modulator
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TPC	Takeda Pharmaceutical Company Limited
UFS-QOL	uterine fibroid symptom and quality of life
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Uterine fibroid is a benign sex hormone-dependent gynecological disease affecting 1 in every 3 to 4 women. Most uterine fibroids are asymptomatic, but clinical symptoms such as increase in menstrual blood loss and anemia due to menorrhagia as well as compression and pain in the bladder and pelvis due to large myoma are seen in about 10% to 20% of patients. In particular, menorrhagia is considered to be caused by the combination of an increase in surface area of the uterine cavity; poor uterine contraction due to myoma; and increased circulation, congestion, or impaired hemostasis due to hypertrophy of the endometrium in the vicinity of the myoma. Persistent menorrhagia is known to induce iron-deficiency anemia. Therefore, menorrhagia is a primary factor that deteriorates the quality of life (QOL) of patients with uterine fibroids.

Gonadotropin-releasing hormone (GnRH) agonists, such as leuprorelin are commonly used for the treatment of benign sex hormone-dependent gynecological diseases, such as endometriosis and uterine fibroids. It is considered that continuous use of a GnRH agonist induces a transient increase in the secretion of gonadotropins (flare up), followed by pituitary and gonadal desensitization that decreases sex hormone secretion. Therefore, GnRH agonists exert therapeutic effects against these diseases by reducing secretion of sex hormones. However, GnRH agonists often cause flare up (temporary worsening of symptoms) and may typically take about 3 to 4 weeks before therapeutic effects begin to emerge. They also cannot be orally administered because they are peptides. For these reasons, the development of a new oral drug that is not associated with temporal worsening of symptoms is awaited for the treatment of these diseases.

TAK-385 has been synthesized at Takeda Pharmaceutical Company Limited (TPC) and is an orally active, nonpeptide, GnRH antagonist with a novel structure. TAK-385 antagonizes GnRH on the GnRH receptors that are present in the pituitary anterior lobe basophiles (secretory cells), and inhibits the GnRH-stimulated secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from these cells. As a result, the drug decreases blood concentrations of hormones, including estradiol (E_2) and progesterone (P), and induces amenorrhea. Therefore, TAK-385 is expected to improve the clinical symptoms observed in patients with uterine fibroids. As TAK-385 is a GnRH antagonist, it causes no flare up and has a faster onset of action than GnRH agonists. Unlike GnRH agonists, which are given either subcutaneously (SC) or intranasally, TAK-385 is a nonpeptide preparation and can be administered orally.

For the above reasons, the development of TAK-385 for the treatment of benign sex hormone-dependent gynecological diseases, such as endometriosis and uterine fibroids, has been progressing in Japan and overseas.

4.2 Rationale for the Proposed Study

A phase 1 study [redacted]

[redacted]

The efficacy and safety of TAK-385 were investigated when orally administered to patients with uterine fibroids at dose levels of 10, 20, and 40 mg for 12 weeks, compared to placebo in the Phase 2 study (TAK-385/CCT-001).

In the efficacy evaluation, a statistically significant difference in proportion of subjects with a total pictorial blood loss assessment chart (PBAC) score of < 10 from Week 6 to 12, as the primary endpoint in the Phase 2 study, was observed between each TAK-385 group and placebo group. The proportion was highest in TAK-385 40 mg group, suggesting a dose-response relationship. The decrease in menstrual blood loss, and achievement of amenorrhea, being ones of the secondary endpoints in this study, was seen in higher proportion of subjects at the higher dose levels of TAK-385 evaluated. In addition, regarding the more direct effects of TAK-385 to the uterine fibroids disease, larger improvement was seen at higher dose also in percent change of myoma and uterine volumes from the early stage of treatment, change in the amount of blood concentration of hemoglobin (HGB). As for pain symptoms in patients with uterine fibroids, the Numerical Rating Scale (NRS) score from Week 6 to 12 was lower in the higher dose of TAK-385. It was, therefore, suggested that the clinical symptoms of patients with uterine fibroids would be improved up to and most greatly in TAK-385 40 mg group.

In the safety evaluation, the common treatment-emergent adverse events (TEAEs) reported during the study period were nasopharyngitis, headache, metrorrhagia, menorrhagia (among the 35 subjects in which the symptoms were categorized as menorrhagia, 34 subjects were actually diagnosed with menostaxis [lowest level term].), genital hemorrhage, menstruation irregular and hot flush. As for the TEAEs relevant to the pharmacological activity of TAK-385, such as hot flush, headache, menstruation irregular, and metrorrhagia, the incidence was higher in accordance with the dose levels among the 10, 20, and 40 mg groups of TAK-385, but there were no clinically significant TEAEs related to the study drug. The percent change of bone mineral density (BMD) in this study was considered to be the same level compared to the percent change of BMD that has previously been reported with the use of leuprorelin 3.75 mg.

Based on the above, a Phase 3 confirmatory study in uterine fibroid patients (TAK-385/CCT-002) was planned to investigate the efficacy and safety of TAK-385 40 mg compared to leuprorelin which is widely used for the treatment of uterine fibroids. In the Phase 2 study, the result showed a trend toward improvement in the NRS score with increasing dose of TAK-385, indicating the possible effect of TAK-385 on pain relief. However, the evaluation was not conducted in patients with pain symptoms associated with uterine fibroids. Therefore, this Phase 3 study was planned to evaluate the efficacy of TAK-385 40 mg compared to placebo in the treatment of pain symptoms associated with uterine fibroids in parallel with the Phase 3 confirmatory study.

Pharmacogenomics (PGx) analysis may be conducted to investigate the contribution of genetic variance on drug response, eg, its efficacy and safety. Participation of study subjects in PGx sample collection is optional.

As PGx is an evolving science, numerous genes and the corresponding functions are currently not yet fully understood. Future data may suggest a role of some of these genes in drug responses or diseases, which may lead to additional hypothesis-generating exploratory research on stored samples.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of TAK-385 40 mg administered orally once daily for 12 weeks, compared with placebo in subjects having pain symptoms associated with uterine fibroids.

5.1.2 Secondary Objective

The secondary objective of this study is to evaluate the safety of TAK-385 40 mg administered orally once daily for 12 weeks, compared with placebo in subjects having pain symptoms associated with uterine fibroids.

5.1.3 Additional Objectives

An additional objective of this study is to evaluate the pharmacodynamic effect, which is blood concentrations of LH, FSH, E_2, and P.

5.2 Endpoints

5.2.1 Primary Endpoint

1) Efficacy:

Proportion of subjects with a maximum NRS (an 11-point scale for patient self-reporting of pain symptoms. The score ranges from 0 to 10.) score of 1or less during the 28 days before the final dose of study drug

5.2.2 Secondary Endpoints

1) Efficacy:

- Proportion of subjects with a maximum NRS score of 0 during the 28 days before the final dose of study drug
- Mean NRS score during the 28 days before the final dose of study drug
- Number of days without pain symptoms (NRS = 0) during the 28 days before the final dose of study drug

2) Safety:

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

5.2.3 Additional Endpoints

- Proportion of days using analgesics during the 28 days before the final dose of study drug

- LH, FSH, E_2 and P (Week 4, 8, 12 and Follow-up)

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

An overview of the study design is shown in Figure 6.a. See Appendix A for details of the schedule of tests, observations, and evaluations.

6.1.1 Study Population and Design

This is a phase 3, multicenter, randomized, double-blind, parallel-group study to evaluate the efficacy of TAK-385 40 mg administered orally once daily for 12 weeks compared with placebo in subjects having pain symptoms associated with uterine fibroids.

Subjects must have a diagnosis of uterine fibroids confirmed by transvaginal ultrasound or other methods. Subjects must experience pain symptoms (eg, lower abdominal pain and low back pain) with intensity of ≥1 on the NRS score for at least 2 days during 1 menstrual cycle, of which at least one of the intensities should be at least moderate (NRS score of ≥4). The total number of subjects to be randomized under double-blind conditions is 64 (32 subjects each for the TAK-385 40 mg group or placebo group).

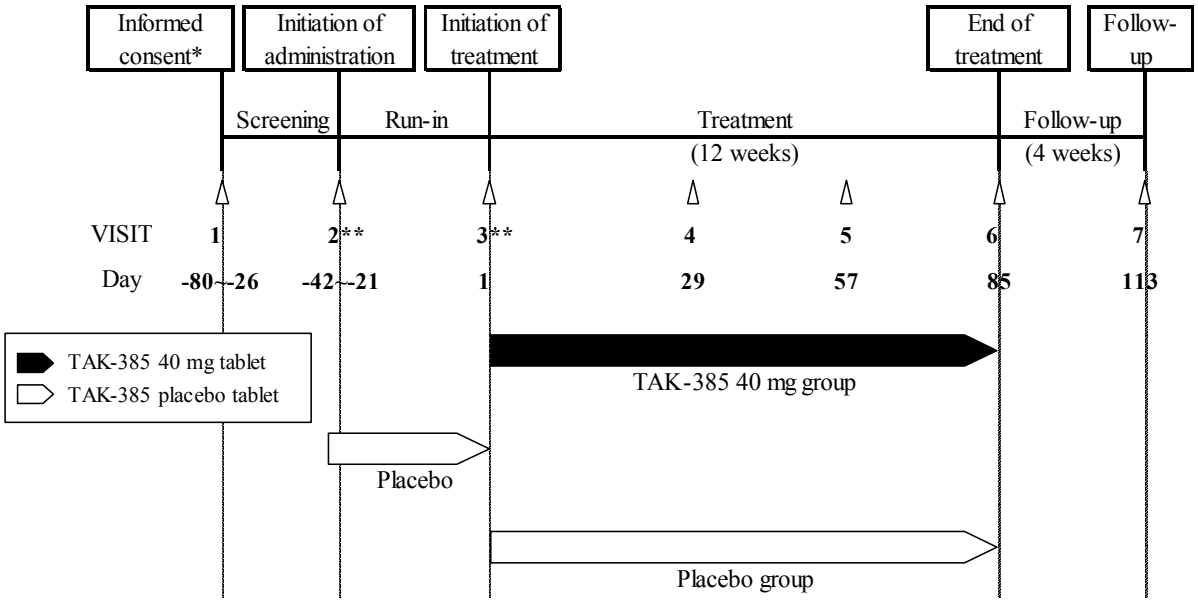
After signing the informed consent form, subjects will start recording in the patient diary from the day of VISIT 1. During the period between VISIT 2 and VISIT 3, in which subjects must experience 1 menstrual cycle, the baseline values for the efficacy evaluation of pain symptoms (baseline NRS score: the maximum NRS score for the entire menstrual cycle immediately before VISIT 3.) will be collected. Subjects should record in the patient diary every day until the end of study drug administration. VISIT 2 should be between the first and fifth day of the first menstruation after VISIT 1. The study drug (TAK-385 placebo) will be administered under single-blind conditions from the day of first menstruation after VISIT 1 to the day before VISIT 3. VISIT 3 should be between the first and fifth day of the second menstruation after VISIT 1. From VISITS 2 to 6, subjects should try to visit the study site during the morning in a fasted state and before taking the study drug.

This study consists of Screening of approximately 1 to 6 weeks, a Run-in period of 3 to 6 weeks, a Treatment period of 12 weeks, and a Follow-up period of 4 weeks. The total period of study participation is approximately 20 to 28 weeks. If the recovery of the first post-treatment menstruation is not observed by the visit at the end of the Follow-up (VISIT 7), the subject will undergo further follow-up using possible means such as by telephone interview, until the recovery of the first post-treatment menstruation is observed. During the course of this study, subjects will visit the study site to undergo the designated examinations and evaluations at each visit.

6.1.2 Dose Level and Regimen

At VISIT 3, subjects will be randomized in a 1:1 ratio to either the TAK-385 40 mg group or placebo group. Study drug (TAK-385 40 mg or TAK-385 placebo) will be administered from the day of VISIT 3 to the day before VISIT 6 (or until early termination) under double-blind conditions.

TAK-385 (or TAK-385 placebo) will be administered daily as a single oral dose before breakfast.



* In addition to Day -80~-26, informed consent may be obtained before Day -80.
**VISIT 2 and 3: On days 1 to 5 of the menstrual cycle

Figure 6.a Schematic of Study Design

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Justification for Study Population and Design

Menorrhagia is the most frequent symptom seen in patients with uterine fibroids. Prolonged menorrhagia can induce iron-deficiency anemia. Therefore, menorrhagia is the main cause of QOL deterioration[1].

Pain symptoms are also known to be important factors that impact the patients' QOL. Pain symptoms in patients with uterine fibroids are observed mostly in menstruation period. However, pain symptoms outside the menstruation period are also observed.

As a result of Phase 2 study (TAK-385/CCT-001), the NRS score from Week 6 to 12 was lower in the higher dose of TAK-385 in patients with uterine fibroids. This result showed a trend toward improvement in the NRS score with increasing dose of TAK-385, indicating the possible effect of TAK-385 on pain relief. However, the efficacy for pain symptoms of TAK-385 is still to be further investigated. For this reason, this study is designed as a double-blind, placebo-

controlled, parallel-group comparison to evaluate the effect of TAK-385 on pain relief in patients with uterine fibroids who have pain symptoms.

The Treatment of this study is set as 3 months for efficacy assessment of primary endpoint because period of general presurgical treatment of myomectomy is 3 months[2]. Additionally, the pain symptoms in patients with uterine fibroids seem to be induced by bleeding, thus a period of approximately 3 months was required to assess the pain symptoms as same as the assessment period of the primary endpoint in pivotal Phase 3 (CCT-002). A single-blind treatment period (with placebo) is also included to investigate if there is any potential placebo effect on baseline pain assessment. In addition, the Follow-up is included for safety assessment, including assessment of the recovery of menstruation after completion of treatment with the study drugs.

6.2.2 Justification for Dose Level and Regimen

The efficacy, safety, pharmacokinetics, and pharmacodynamics of TAK-385 10, 20, and 40 mg were evaluated in study TAK-385/CCT-001. For the primary endpoint (proportion of subjects with a total PBAC score of <10 from Week 6 to 12), statistically significant differences were observed in all TAK-385 treatment groups compared to placebo group. The proportion was higher in the TAK-385 40 mg group compared to the other treatment arms, suggesting a dose-response relationship. Similarly, the trend toward improvement with increasing dose was also observed in the secondary endpoints, change in myoma and uterine volumes, blood concentration of HGB and pain symptoms. The common TEAEs were considered to be caused by the pharmacological effect of TAK-385, and their incidence was higher in the TAK-385 treatment groups compared to placebo group. Most of the TEAEs were mild or moderate, and no serious TEAEs considered related to the study drug were observed. A trend toward a decrease in BMD was observed with increasing dose. However, the type, frequency, and intensity of TEAEs and the percent change of BMD were expected to be at a comparable level as that of GnRH agonists; therefore, there seemed to be no clinically serious problem on safety. For these reasons, the dose of 40 mg is considered appropriate for use as the clinical dose of TAK-385 to evaluate the efficacy and safety in subjects with uterine fibroids.

[redacted] TAK-385 will be administered once daily before breakfast.

6.2.3 Justification for Endpoints

6.2.3.1 Primary Endpoint

Pain experienced in patients with uterine fibroids can be categorized as pain caused by bleeding, pain triggered by twisted myoma or pain associated with compression of the organ by enlarged fibroids. Pain can emerge only during menstruation or can be chronic, and the frequency of pain varies among patients. However, in all of the above cases, QOL is most affected by the “grade” of pain in patients with uterine fibroids who have pain symptom. Therefore, assessment of the

highest score in pain assessment scale is considered appropriate to evaluate the efficacy of TAK-385. Subjects with a maximum NRS score of ≥4 (ie, subjects with at least "moderate" pain symptoms) and who have pain symptoms of at least 2 days, in 1 menstrual cycle just before VISIT 3 will be regarded as possessing pain symptoms associated with uterine fibroids, and can be included into this study. The "proportion of subjects with a maximum NRS score of 1 or less during the 28 days before the final dose of study drug" is to be evaluated as primary endpoint. As for evaluating the improvement of pain symptoms, it is considered to be preferable to confirm the loss of pain symptoms. However, drug therapy for uterine fibroids is not a curative therapy and uterine fibroids would not disappear after TAK-385 administration. Also, it is often difficult for the subjects who have the pain symptoms to distinguish where their pain occured, and the possibility that some patients record slight uncomfortable feeling as the pain symptoms associated with uterine fibroids is undeniable. From these reasons, it is not necessarily appropriate to set the loss of pain symptoms as primary endpoint to evaluate the pain-ameliorating effect in TAK-385. Therefore, the cut-off value of 1, which is the lowest score of NRS in patients with pain symptoms, was set for evaluating the improvement of pain symptoms. Three or more changes as NRS score could be found by setting this endpoint. Since the average menstrual cycle in Japanese women is 28 days long, the pain score is to be evaluated in 28 days.

For these reasons, "proportion of subjects with a maximum NRS score of 1 or less during the 28 days before the final dose of study drug" is selected as the primary endpoint.

6.2.3.2 Secondary Endpoints

In order to assess the loss of pain symptoms, "proportion of subjects with a maximum NRS score of 0 during the 28 days before the final dose of study drug" (ie, proportion of subjects with "no pain" during the 28 days before the final dose of study drug) is to be evaluated.

The mean NRS score is designated to assess overall pain symptoms in a single menstrual cycle.

Additionally, the number of days without pain symptoms (NRS = 0) during the 28 days before the final dose of study drug is designated to assess frequency of pain symptoms.

Other commonly used safety endpoints, such as AEs and vital signs, are also included.

6.2.3.3 Additional Endpoints

Furthermore, the proportion of days using analgesics is also assessed since patients who experience pain symptoms usually use analgesics.

For the additional evaluation of the safety and efficacy of TAK-385 and pharmacodynamics of TAK-385 (LH, FSH, E_2, and P concentrations) in subjects with uterine fibroids are also to be evaluated.

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 medication that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (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

A study 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 Sites

In the event that the sponsor, an institutional review board (IRB) 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 entry criteria, including test results, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study.

7.1.1 Inclusion Criteria for Entering the Screening (at VISIT 1)

1. In the opinion of the investigator or subinvestigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form prior to the initiation of any study procedures.
3. Prior to VISIT 1, the subject has a diagnosis of uterine fibroids confirmed by transvaginal ultrasound, abdominal ultrasound, magnetic resonance imaging (MRI), computed tomography (CT), or laparoscopy, and has never received surgical treatment for the myoma (measurable noncalcified myoma with a longest diameter of ≥3 cm).
4. The subject is a premenopausal Japanese woman.
5. The subject is aged 20 years or older on the day of signing and dating the informed consent form.
6. The subject has 1 or more measurable noncalcified myomas with a longest diameter of ≥3 cm confirmed by transvaginal ultrasound.
7. The subject has experienced 1 or more regular menstrual cycles (25 to 38 days) immediately prior to VISIT 1 and that should include menstrual bleeding of at least 3 consecutive days.
8. The subject who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception from signing of informed consent throughout the duration of the study.

*Definitions and acceptable methods of contraception are defined in Section 9.1.9 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.10 Pregnancy.

7.1.2 Inclusion Criteria for Entering the Run-in (at VISIT 2)

9. The subject has experienced regular menstrual cycles (25 to 38 days) immediately prior to VISIT 2 that should include menstrual bleeding of at least 3 consecutive days (at least 2 regular menstruation cycles to be confirmed by Inclusion criteria #7 and #9).

7.1.3 Inclusion Criteria for Entering the Treatment (at VISIT 3)

10. The subject has 1 or more measurable noncalcified myomas, with a longest diameter of ≥3 cm confirmed by transvaginal ultrasound (the same myoma should be measured as in Inclusion criterion #6).
11. The subject has a maximum NRS score of ≥4 in 1 menstrual cycle just before VISIT 3.
12. The subject has pain symptoms associated with uterine fibroids of at least 2 days in 1 menstrual cycle just before VISIT 3.
13. The subject has experienced regular menstrual cycles (25 to 38 days) after VISIT 1 that should include menstrual bleeding of at least 3 consecutive days (at least 3 regular menstruation cycles to be confirmed by Inclusion criteria #7, #9 and #13).

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study.

1. The subject has received any investigational compound within 24 weeks prior to the start of the administration of the study medication for the day of first menstruation after VISIT 1.
2. The subject has received TAK-385 (including placebo) in a previous clinical study.
3. The subject is an immediate family member, study site employee, or is in a dependant relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
4. The subject has lower abdominal pain due to irritable bowel syndrome or severe interstitial cystitis.
5. The subject has a current history of thyroid gland disorder with irregular menstruation, or has a potential for irregular menstruation due to thyroid gland disorder, as determined by the investigator or subinvestigator.
6. The subject has a previous or current history of pelvic inflammatory disease within the 8 weeks prior to VISIT 1.
7. The subject has a positive Pap smear test result conducted within the 1 year prior to VISIT 1 (if there are no previous test results, those who were judged positive in the test conducted before VISIT 2).

   Note: “Positive” is defined as the result that falls in classes other than I or II in the Nichibo Classification or any result other than negative for intraepithelial lesion or malignancy (NILM) in the Bethesda System.
8. The subject has a history of panhysterectomy or bilateral oophorectomy.
9. The subject has had markedly abnormal uterine bleeding or anovulatory bleeding, as determined by the investigator or subinvestigator.

10. The subject has a malignant tumor or a history of a malignant tumor within the 5 years prior to VISIT 1.
11. The subject has been treated with selective estrogen receptor modulators (SERMs) (excluding drugs for external use and dietary supplements) within the 4 weeks prior to VISIT 2.
12. The subject has been treated with any of the following drugs within the 8 weeks prior to VISIT 2: oral contraceptive or sex hormone preparations (norethindrone, norethisterone, medroxyprogesterone, estrogen, or other progestins), and within the 16 weeks prior to VISIT 2: GnRH analogues, dienogest, danazol, or aromatase inhibitors (for 1- and 3-month sustained-release preparations, within the 20 and 28 weeks prior to VISIT 2, respectively).
13. The subject has a previous or current history of severe hypersensitivity or severe allergies to drugs.
14. The subject has nondiagnosable abnormal genital bleeding.
15. Female subject who is pregnant, lactating, or intending to become pregnant or to donate ova prior to signing of informed consent, during the study period, or within 1 month after the end of the study.
16. The subject has clinically significant cardiovascular disease (eg, myocardial infarction or unstable angina pectoris within the 24 weeks prior to VISIT 1) or uncontrollable hypertension (eg, resting systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg at Screening and Run in).
17. The subject is inappropriate for participation in this study based on standard 12-lead ECG findings, as determined by the investigator or subinvestigator.
18. The subject has active liver disease or jaundice, or with alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin (total bilirubin) >1.5 times the upper limit of normal (ULN) in the clinical laboratory tests at VISIT 1 and 2.
19. The subject has previous or current history of diseases considered to be inappropriate for participation in this study, including severe hepatic impairment, jaundice, renal impairment, cardiovascular disease, endocrine system disease, metabolic disorder, pulmonary disease, gastrointestinal disease, neural disease, urological disease, immune disease, or mental disorder (especially depression-like symptoms) or suicide attempt resulting from a mental disorder.
20. The subject has a previous or current history of drug abuse (defined as any illicit drug use) or alcohol abuse.
21. The subject is inappropriate for participation in this study for other reasons, as determined by the investigator or subinvestigator.

7.3 Excluded Medications and Treatments

7.3.1 Excluded Medications

Use of the following drugs is prohibited in this study.

7.3.1.1 Sex Hormone and Anti-hormone Preparations

Use of the following drugs is prohibited from VISIT 1 to 7 (or until early termination) to avoid confounding of the assessment of safety, efficacy and pharmacodynamics.

- Danazol
- GnRH analogues
- Dienogest
- Oral contraceptives and other sex hormone preparations (norethindrone, norethisterone, medroxyprogesterone, estrogen, and other progestins)
- Aromatase inhibitors
- Herbal medicines with indications related to menstruation (eg, Tokishakuyakusan and Keishi-bukuryogan)

7.3.1.2 Other Drugs That May Affect Efficacy, Safety, or Pharmacokinetic Assessment of TAK-385

Use of the following drugs (excluding drugs for external use and dietary supplements) is prohibited from VISIT 1 to 6 (or until early termination).

- Steroid hormones
- Anti-epileptic drugs
- Anti-convulsants
- Anti-depressants
- Anti-psychotics (major tranquilizers)
- Ergot alkaloids
- St. John's wort (Hypericum perforatum)
- P-glycoprotein (P-gp) inhibitors
- P-gp inducers
- Cytochrome P450 inducers
- SERMs
- Analgesics (excludes those specified in Section 7.3.2; use of external preparations for the treatment of pain not associated with uterine fibroids is permitted)

7.3.2 Drugs Permitted with Condition

Use of analgesics is **ONLY permitted under the following conditions** from VISIT 1 to 6 (or until early termination). This restriction was set because it is likely to have an impact on the evaluation of primary, secondary and additional endpoints. Analgesics refer to drugs containing compounds that have indications for pain symptoms in the package inserts and antispasmodic drugs which possess indications for gynecological or urological disease in the package inserts.

- For severe pain **associated with uterine fibroids**; Loxoprofen can be used as the first choice medicine. If loxoprofen cannot be used for various reasons, other non-steroidal anti-inflammatory drugs (NSAIDs) can be used.
- For treatment of AE, etc. **NOT associated with uterine fibroids** (eg, common cold); Acetaminophen can be used as the first choice medicine. If acetaminophen cannot be used for various reasons, other NSAIDs can be used. In addition to acetaminophen and NSAIDs, analgesics for external use are also permitted to be used.

Analgesics for pain associated with uterine fibroids will be provided by the site in accordance with the approved package labeling.

The investigator or subinvestigator should instruct subjects to take analgesics as directed and to avoid using them under a fasted state. The investigator or subinvestigator should instruct subjects not to casually use analgesics for prophylactic purposes. The investigator or subinvestigator should also instruct subjects to record their maximum pain symptoms during the past 24 hours, considering pain symptoms before taking analgesics, in the patient diary (NRS). Subjects must record the use of analgesics to relieve pain from uterine fibroids every day in the patient diary.

In addition, analgesics can be used in the cases as follows.

- When the reason for use is other than AE, concurrent condition or target disease (eg, scopolamine butylbromide for MRI preparation)
- Codeine which is not intended to relieve pain associated with uterine fibroids (eg, codeine phosphate in a combination cold remedy)

7.3.3 Excluded Treatments

Surgical treatment of uterine fibroids, and use of intrauterine device (IUD) are prohibited from VISIT 1 to VISIT 7 (or until early termination).

7.4 Diet, Fluid and Activity Control

The investigator, subinvestigator, and study collaborator should advise subjects to comply with the following instructions:

1. Make the scheduled visits on time, and undergo examinations and tests as requested. If the subject cannot make a scheduled visit, she should inform the study site as soon as possible.
2. Report the subjective symptom and objective symptom at each visit, including its contents, the date of occurrence, intensity, outcome, and date of outcome.

3. If any abnormality has occurred between visits, such as worsening of a bleeding symptom, the subject should immediately report to the investigator, subinvestigator, or study collaborator by telephone or other means, and ask for instructions.
4. If the subject visits another medical institution during the study period, she should inform the investigator or subinvestigator about the reasons for the visit and treatment received.
5. If the subject takes any drugs other than those prescribed by the investigator or subinvestigator (including over-the-counter medications), she should report this at the next visit.
6. The subject should record in the patient diary every day (keeping a daily record of pain symptoms and entering information on the use of study drugs and analgesics are very important for the evaluation of TAK-385 in this study).
7. The subjects are instructed to use adequate contraception during the study period.
8. The subjects will be asked to avoid excessive exercise and activities, and maintain a normal daily routine during the study period. In particular, subjects must avoid drinking and eating excessively on the day before each visit, and should also avoid drinking grapefruit juice to any extent possible during the study period.
9. The subject should bring all unused study drugs, empty blister card(s) of study drug, and the patient diary to each visit.
10. The subject should start taking the study drug on the day of first menstruation after VISIT 1, and start taking the study drug for the Treatment from the day of VISIT 3. The subject should take the study drug every day as instructed by the investigator or subinvestigator. Taking the study drug every day is very important for the drug to show its expected effects.
11. The subject should take study drugs every day before breakfast during the Run-in and the Treatment, and should try to take the study drug at approximately the same time each day. If the subject forgets to take the study drug before breakfast, she should take it before lunch on the same day. If the subject forgets to take the study drug in both cases (ie, before breakfast and before lunch), she should take it before dinner on the same day. The subject should avoid carrying over the missed dose to other day and taking multiple doses together on the same day. The date of administration and whether the drug was taken before a meal should be properly recorded in the patient diary.

    For the scheduled study site visit from VISIT 2 through 6, follow the instructions below:

    <VISIT 2, 3 and 6>

    On the days of the scheduled study site visit, the subject should try to visit the study site without taking the TAK-385 tablet in the morning and undergo the designated study procedures as far as possible. Even if the subject cannot visit the study site in the morning, she should still come to the study site without taking the TAK-385 tablet.

<VISIT 4 and 5>

On the days of the scheduled study site visit, the subject should try to visit the study site without taking the TAK-385 tablet in the morning and undergo the designated study procedures as far as possible. If the subject cannot visit the study site in the morning, she must take the TAK-385 tablet before breakfast, and report to the investigator or subinvestigator that she has taken the drug.

12. When the subject needs to take analgesic drugs due to severe pain associated with uterine fibroids, the subject should comply with the investigator's or subinvestigator's instructions before taking the analgesic drug, and try to avoid taking it in a fasted state as far as possible. The subject should also not take the analgesic drug casually or for prophylactic purposes. In cases where the subject has to take an analgesic drug, she is required to properly record her pain symptoms which occur before taking analgesics in the patient diary (NRS) and to record analgesic use in the patient diary.
13. The subject may use acetaminophen as the first choice medicine in certain circumstances, such as occurrence of an AE, that requires an analgesic for purposes other than to relieve pain from uterine fibroids. In this case, avoid casually using it for prophylactic purposes.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the electronic case report form (eCRF) using the following categories. For subject failure, refer to Section 9.1.14.

1. Death. The subject died on study and caused early termination of study treatment.

Note: If the subject dies on study, the event will be considered as serious adverse event (SAE). Refer to Section 10.2.2 for the reporting procedures.

2. Adverse event (AE). The subject has experienced an 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 AE.

- Liver Function Test (LFT) Abnormalities

  Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.8), if the following circumstances occur at any time during study medication treatment:

  – ALT or AST >8 ×ULN, or
  – ALT or AST >5 × ULN and persists for more than 2 weeks, or
  – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
  – ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

- Hypoestrogenic symptoms

  The investigator or subinvestigator makes an overall risk-benefit assessment for the subject when any of the following events that can be considered related to the pharmacological effect of TAK-385 occur, and decides whether to stop the drug administration based on the intensity and frequency of the event:

  – Hot flush, feeling hot, flushed face, shoulder stiffness, headache, insomnia, dizziness, perspiration, menopausal depression, decreased libido, feeling cold, visual disturbance, emotional lability.

- ECG abnormality

  The subject judged by the investigator or subinvestigator to be inappropriate for continuation of the study based on standard 12-lead ECG findings.

3. Protocol deviation. The discovery after randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
5. Withdrawal by subject. 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 (withdrawal due to an AE or lack of efficacy should not be recorded in the "Withdrawal by subject" category).

6. Study terminated by sponsor. The sponsor terminates the study.
7. Pregnancy. The subject is found to be pregnant.

Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.10.

8. Lack of efficacy. The investigator or subinvestigator judges TAK-385 shows no efficacy based on the menstrual blood loss, menstrual status, and use of analgesics (eg, a notable increase in the frequency of taking analgesics due to intolerable pain after start of study drug administration) and judges continued participation in the study would pose an unacceptable risk to the subject.
9. Other.

Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator or subinvestigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue her participation without giving a reason at any time

during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator or subinvestigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials 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 Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Investigational Drug

Study drug name: TAK-385

Nonproprietary name: relugolix (international non-proprietary name [INN])

Chemical name:

Urea, N-[4-[1-[(2,6-difluorophenyl)methyl]-5-[(dimethylamino)methyl]-1,2,3,4-tetrahydro-3-(6-methoxy-3-pyridazinyl)-2,4-dioxothieno[2,3-d]pyrimidin-6-yl]phenyl]-N'-methoxy-

Dosage form and content:

Name	Content
TAK-385 40 mg tablet	Contains 40 mg of TAK-385 per tablet
TAK-385 placebo tablet	Contains no TAK-385 per tablet

Appearance: both the TAK-385 40 mg tablet and TAK-385 placebo tablet are light yellow red, film-coated tablets and are indistinguishable in appearance from each other.

8.1.1.2 Packaging and Labeling

1. Packaging of study drugs for the Run-in (single-blind)

TAK-385 placebo tablets are packaged in blister cards containing 14 tablets (for 14 days) per sheet. Three blister cards are sealed in an aluminum pouch with desiccant. Three aluminum pouches, each containing 3 blister cards, are placed in an outer case. One pouch is allocated to each subject.

The outer case indicates that it contains a study drug and includes the name of the drug, quantity, protocol number, sponsor's name and address, serial number, and storage conditions.

2. Packaging of study drugs for the Treatment (double-blind)

TAK-385 40 mg tablets or TAK-385 placebo tablets are packaged in blister cards containing 14 tablets (for 14 days) per sheet. Three blister cards are sealed in an aluminum pouch with desiccant. Three aluminum pouches, each containing 3 blister cards, are placed in an outer case. One outer case is allocated to each subject. All packaging materials for TAK-385 40 mg tablets and TAK-385 placebo tablets are indistinguishable from each other.

The outer case indicates that it contains a study drug, and includes the name of the drug, quantity, protocol number, sponsor's name and address, serial number, and storage conditions.

8.1.2 Storage

Investigational drug referred in 8.1.1.1 are to be kept at room temperature (1°C to 30°C). A daily temperature log of the drug storage area must be maintained every working day.

Investigational drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Investigational drug must be stored under the conditions specified on the label, and remain in the original container until dispensed.

8.1.3 Dose and Regimen

Table 8.a describes the dose and tablet count that will be provided to each group.

Table 8.a Dose and Regimen

Period	Group	Dose and Regimen
Run-in	All group	One TAK-385 placebo tablet per day
Treatment	TAK-385 40 mg group	One TAK-385 40 mg tablet per day
	Placebo group	One TAK-385 placebo tablet per day

1. Run-in

Administration of TAK-385 placebo tablets should be started on the day of first menstruation after VISIT 1. Until the day before VISIT 3, subjects take 1 tablet once daily before breakfast. The investigator or designee must instruct the subject to bring each of the study drug containers (blister cards) to each visit, regardless of whether the study drugs are empty.

2. Treatment

Administration of TAK-385 40 mg tablets or TAK-385 placebo tablets should be started on the day of VISIT 3. Until the day before VISIT 6, subjects take 1 tablet once daily before breakfast. During the Treatment, subjects should try to make each scheduled visit to the study site in the morning and take the TAK-385 (40 mg or placebo) tablet for the day after completing the scheduled tests (see Section 7.4). However, if unable to visit the study site in the morning of VISIT 4 or 5, subjects should take the morning dose before breakfast and report to the investigator or subinvestigator that the morning dose has been taken (see Section 7.4).

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 overdosing study drug during the treatment period (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 CRFs according to Section 10.0, ADVERSE EVENTS.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Investigational Drug Assignment and Dispensing Procedures

The investigator or his/her designee assigns the investigational drug to the subject in numerical order of the drug number in each site, and the study drug set with the number is dispensed to the subject. The investigator or his/her designee enters the study drug number in the eCRF.

8.3 Randomization Code Creation and Storage

The supervisor on randomization personnel generates a randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

At VISIT 3, subjects will be randomized in a 1:1 ratio to either the TAK-385 40 mg group or placebo group.

8.4 Investigational Drug Blind Maintenance

The emergency key control center will keep the emergency key until it needs to be accessed in an emergency or the database for all subjects is locked.

Blind maintenance may become difficult in this study depending on the results of pharmacodynamic testing. For blind maintenance, the laboratory conducting the analysis should conceal the test results from any outside party until the randomization code is opened. The laboratory reports the results to the investigator via the sponsor after the randomization code is opened. If the test results need to be reported before the randomization code is opened, the necessary steps for of blind maintenance must be taken not to be identified the subject by a person appointed at the laboratory, such as changing the drug numbers. The test results may then be reported to the sponsor via the randomization personnel of the sponsor or the designee.

During the period between the day of first menstruation after VISIT 1 and VISIT3, all subjects will receive the placebo treatment in a single-blind manner. Subjects must not be informed of their treatment allocation (placebo) during this time as it may compromise study data.

8.5 Unblinding Procedure

The investigational drug blind should not be broken by the investigator or subinvestigator unless information concerning the investigational drug is necessary for the medical treatment of the subject.

The investigator or subinvestigator may obtain the randomization information to break the blinding by contacting the emergency key control center (see the contact information in the attachment).

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the document called Record of Early Blind-Breaking and the same information (except the time) must be recorded on the eCRF.

If any site personnel is unblinded, investigational drug must be stopped immediately and the subject must be withdrawn from the study.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

The site designee will receive the procedures for handling, storage and management of investigational medicines created by the sponsor, according to which the site designee will appropriately manage the sponsor-supplied drug (TAK-385 placebo tablet for the Run-in, TAK-385 40 mg tablet or TAK-385 placebo tablet for the Treatment). The investigator will also receive those procedures from the sponsor. The procedures include those for ensuring appropriate receipt, handling, storage, management, dispensation of the sponsor-supplied drug, and collection of unused medications from the subject as well as return of them to the sponsor or destruction of them.

The site designee will immediately return unused medications to the sponsor after the study is closed at the site.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator and subinvestigator whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

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

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is explained; this subject number will be used throughout the study.

9.1.1.1 Pharmacogenomic Informed Consent Procedure

A separate informed consent form pertaining to storage of the sample must be obtained prior to collecting a blood sample for PGx research for this study. 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 Medication History Procedure

Demographic information to be obtained will include date of birth, sex, birth history, classification of uterine fibroids, first defined diagnosis date of uterine fibroids, treatment history of uterine fibroids and smoking classification of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases that stopped within one year prior to signing of informed consent. All events related to the exclusion criteria must be surveyed regardless of the time of resolution or disappearance. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7).

Medication history information to be obtained includes any medication that was stopped at or within 4 weeks (28 days) prior to signing of informed consent.

9.1.3 Physical Examination Procedure

The following body systems will be examined.

(1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) genitourinary system; and (12) other.

All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination.

9.1.4 Weight, Height and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The body mass index (BMI) is calculated by the sponsor from the weight and height recorded in the eCRF using metric units with the formula provided below. The Takeda standard for collecting height is centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: BMI = weight (kg)/height $(m)^2$

Example:

Height = 176 cm, Weight = 79.2 kg, BMI = $79.2/1.76^2 = 25.6$ kg/m^2

9.1.5 Vital Sign Procedure

Vital signs will include body temperature (axilla measurement), sitting blood pressure (resting ≥5 minutes), and pulse (beats per minute).

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through VISIT 7 [or early termination]), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

9.1.7 Documentation of 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, standard 12-lead ECG, or physical examination abnormalities noted at screening examination. The condition (ie, diagnosis) should be described.

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 17 mL (including PGx sample collection), and the approximate total volume of blood for the study is 85 mL (including PGx sample collection).

The samples collected for clinical laboratory tests are listed in Table 9.a.

Table 9.a Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis
Red blood cells (RBC) White blood cells (WBC) with differential HGB Hematocrit (HCT) Platelets	ALT AST Lactate dehydrogenase (LDH) Gamma glutamyl transferase (GGT) Albumin Alkaline phosphatase (ALP) Bilirubin (Total bilirubin) Protein (Total protein) Cholesterol (Total cholesterol) High density lipoprotein (HDL) cholesterol Low density lipoprotein (LDL) cholesterol Triglyceride Glucose HGB A1C Creatinine Blood urea nitrogen (BUN) Creatine kinase Urate Sodium Potassium Chloride Calcium Phosphate Magnesium	Qualitative (protein, glucose, occult blood, urobilinogen, bilirubin) Pregnancy test (human chorionic gonadotropin [hCG])
Hormone		
LH FSH E_2 P		

The central laboratory (see the attachment 1) will perform laboratory tests for hematology, chemistries, urinalysis (excluding pregnancy test) and hormone.

Each study site will conduct urine pregnancy tests (hCG).

The results of laboratory tests will be returned to the investigator or subinvestigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, ALP, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days

and preferably within 48-72 hours after the abnormality was noted. In this case, "LFT Abnormalities" are to be reported as AEs of special interest (AESI)s.

The investigator will maintain a copy of the reference ranges (with the record of the reference ranges) for the laboratory used.

(Please see Section 7.5 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal LFTs in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.)

9.1.9 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and until the recovery of menstruation after last dose of study medication, subjects who are sexually active with a nonsterilized male partner (sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate) must use adequate contraception. In addition they must be advised not to donate ova during this period.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, where medications and devices containing hormones are excluded, the only acceptable methods of contraception are:

Barrier methods (each time the subject has intercourse):

- Male condom PLUS spermicide.
- Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide.
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and donation of ova during the course of the study.

During the course of the study, regular urine hCG pregnancy tests will be performed, and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Appendix A).

In addition to a negative urine hCG pregnancy test at Screening (VISIT 1), subjects also must have a negative urine hCG pregnancy test at VISIT 2 and VISIT 3.

9.1.10 Pregnancy

If any subject is found to be pregnant during the study, she should be withdrawn and any sponsor-supplied drug should be immediately discontinued.

If the pregnancy occurs during administration of active study medication, eg, after VISIT 3 or within 28 days of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in the attachment 1.

Should the pregnancy occur during or after administration of blinded drug, the investigator or subinvestigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator or subinvestigator.

If the female subject agrees to the primary care physician (obstetrician or gynecologist, etc.) being informed, the investigator or subinvestigator should notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All pregnancies in subjects on active study drug including comparator will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.11 ECG Procedure

A standard 12-lead ECG will be recorded. The investigator or subinvestigator (or a qualified observer at the investigational site) will interpret the ECG using 1 of the following categories: normal or abnormal. The investigator or subinvestigator will judge if it is clinically significant.

9.1.12 Pharmacogenomic Sample Collection

For possible exploratory investigation of markers enabling the prediction of drug response, one 5 mL whole blood sample for PGx should be collected at the earliest time possible between VISIT 3 and VISIT 7 (or early termination) from consenting subject after investigational drug was assigned.

PGx sample should not be collected from any subject who has received comparable bone marrow transplant or whole blood transfusion within 6 months before any sample collection.

See the separately created procedure for directions on collecting, handling, and storage of PGx samples.

9.1.13 Pharmacodynamics Sample Collection

LH, FSH, E_2, and P concentrations are used in the pharmacodynamic evaluation. These sex hormone concentrations are determined using samples collected at each visit from VISIT 3 to 7 (or early termination). To maintain blinding, sex hormone concentrations should be reported to the investigator and sponsor after unblinding.

9.1.14 Documentation of Subjects Failure

An eCRF is completed for each subject who signs informed consent and discontinues study before randomization.

The primary reason for subject failure is recorded in the eCRF using the following categories:

- Death

- Adverse Event
- Screen Failure (failed inclusion criteria or did meet exclusion criteria)
- Protocol deviation
- Lost to follow-up
- Withdrawal by subject <specify reason>
- Study terminated by sponsor
- Pregnancy
- Other <specify reason>

Subject numbers assigned to subjects who fail screening should not be reused.

9.1.15 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is found to be not eligible for randomization, the investigator or subinvestigator should record the primary reason for failure on the applicable eCRF.

9.1.16 Transvaginal Ultrasound

Transvaginal ultrasound is performed for diagnosis of uterine fibroids, and to determine uterine and myoma volumes. To avoid interobserver and interdevice variations, 1 physician (investigator or subinvestigator) will be assigned to a subject and perform all the transvaginal ultrasound scans using the same device as far as possible. Only the largest myoma among those measurable at VISIT 1 will be measured throughout the study.

On the assumption that the uterus and myoma are spheroids, uterine and myoma volumes are calculated using 3 diameters (D1, D2, and D3) measured as shown below:

- D1: the longest diameter of the myoma or uterus (unit of length: cm)
- D2: the longest diameter of the myoma or uterus which is perpendicular to D1 (unit of length: cm)
- D3: the diameter of the myoma or uterus which crosses the intersection of D1 and D2 (intersection “Z”) and is perpendicular to D1/D2 plane (unit of length: cm)

[Formula] Uterine or myoma volume = $D1 \times D2 \times D3 \times \pi / 6$

The investigator or subinvestigator records the D1, D2, and D3 values for the uterus and myoma in the eCRF. With regard to measurement of myoma at VISIT 1, the longest diameter (D1) of the largest myoma is determined and recorded in the eCRF.

See the separate procedure manual regarding details of the transvaginal ultrasound.

9.1.17 Pain Symptoms, Other Clinical Symptoms, and QOL

Pain symptoms are evaluated using the NRS score. The investigator or subinvestigator distributes the patient diary to consented subjects. Subjects fill out the patient diary every day from VISIT 1 to the day before VISIT 6 (or until early termination). Subjects record pain symptoms within 24 hours associated with uterine fibroids (NRS score), menstruation, and use of analgesics. If subjects use any analgesics for pain associated with uterine fibroids, they should record this fact in the patient diary along with the accompanying pain symptoms before use of analgesics. The start/end date of menstruation must be recorded in CRF in reference to the patient diary by the investigator or subinvestigator. If there is anything unclear or insufficient description in the patient diary, queries may be made to the subject, and corrections to the patient diary are recorded by the subject in a change history that captures the old information, the new information, identification of the person making the correction and the date of the correction. If it is impossible to make queries to the subject at site visits, queries will be made to the subject with telephone calls or other means, and corrections to the patient diary are recorded by the investigator or subinvestigator in an change history that captures the old information, the new information, identification of the person making the correction and the date of the correction.

The uterine fibroid symptom and QOL (UFS-QOL) score is used to evaluate other clinical symptoms and the QOL of subjects. The investigator or subinvestigator distributes the UFS-QOL questionnaire at VISITS 3 and 6, and has subjects fill it out before physical examination at site visit.

9.1.18 Status of Menstruation Recovery

If the first menstruation after the end of study drug administration is observed before the VISIT 7 in the Follow-up, the date of onset of the first menstruation is recorded in the eCRF. If menstruation recovery is not observed by the VISIT 7 in the Follow-up, follow-up will be continued as far as possible through telephone calls or other means until the recovery of the first menstruation. If menstruation recovery is observed during continued follow-up, the date of recovery should be recorded in the eCRF. The status at the end of menstruation follow-up will be recorded in the eCRF regarding menstruation recovery. After the Follow-up, follow-up will not be continued in subjects who undergo surgery or receive hormone therapy for the treatment of uterine fibroids before the recovery of menstruation.

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring all remaining study medication and the blister card to each site visit. The investigator or subinvestigator records the start date and end date of administration in the eCRF during the Run-in period and Treatment period. Additionally, the dates of missed study medication administration during the Treatment period are recorded in the eCRF.

If a subject is persistently noncompliant with the study medication (TAK-385 40 mg tablet or TAK-385 placebo tablet) (eg, failure to take 10% or more of the scheduled doses after the last visit), it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time points.

9.3.1 Screening and Run-in

9.3.1.1 VISIT 1 (Day -80 through Day -26)

Subjects undergo examinations and tests for eligibility assessment at VISIT 1 (between 80 and 26 days prior to the initial dose of the study drug for the Treatment). Subject eligibility is determined based on the inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.14 for procedures for documenting the records of subjects withdrawn before study drug administration in the Screening and Run-in. Study drugs for the Run-in are started in single-blind conditions from the day of first menstruation after VISIT 1.

The following procedures should be performed at VISIT 1:

- Informed consent
- Inclusion and exclusion criteria
- Pap smear test (if a subject has no test result obtained within 1 year before VISIT 1, perform pap smear test between VISIT 1 and VISIT 2)
- Demographics and concurrent medical conditions
- Medical history and medication history
- Pregnancy test (urine)
- Physical examination
- Vital signs, height and weight
- Patient diary (distributed)
- Transvaginal ultrasound (see Section 9.1.16. If it cannot be performed at VISIT 1, it may be delayed up to the day before VISIT 2 [but should be done as early as possible])
- Clinical laboratory tests
- Standard 12-lead ECG
- AE
- Concomitant medications
- Dispensing of study drugs for the Run-in

9.3.1.2 VISIT 2 (Day -42 through Day -21)

The subject visits the study site between the first and fifth day of their first menstruation after VISIT 1, without taking the study drug for the Run-in in the morning. The subject should be

screened in accordance with the inclusion and exclusion criteria as described in Section 7.0, including confirmation of the description in the patient diary. See Section 9.1.14 for procedures for documenting the records of subjects withdrawn in the Screening and Run-in.

The following procedures should be performed at VISIT 2:

- Inclusion and exclusion criteria
- Pap smear test (if a subject has no test result obtained within 1 year before VISIT 1, perform pap smear test between VISIT 1 and VISIT 2)
- Pregnancy test (urine)
- Physical examination
- Vital signs and weight
- Patient diary (collected and distributed)
- Clinical laboratory tests
- AE
- Concomitant medications

9.3.2 Treatment

9.3.2.1 VISIT 3 (Day 1)

The subject visits the study site between the first and fifth day of the second menstruation after VISIT 1, without taking the study drug for the Run-in in the morning.

Subjects who satisfy all of the inclusion criteria and do not meet the exclusion criteria are randomized in the manner described in Section 8.2. Study drugs for the Treatment are started on the day of VISIT 3. If a dose is missed before breakfast, subjects may take the TAK-385 tablet before lunch on the same day. If a dose is missed before breakfast and lunch, subjects may take the TAK-385 tablet before dinner on the same day. The procedure for documenting the records of subjects withdrawn before randomization is provided in Section 9.1.14. Subjects are randomized after eligibility assessment on Day 1 (VISIT 3).

The following procedures should be performed at VISIT 3:

- Inclusion and exclusion criteria
- Pregnancy test (urine)
- Physical examination
- Vital signs and weight
- Patient diary (collected and distributed)
- Transvaginal ultrasound (see Section 9.1.16. If it cannot be performed at VISIT 3, it is performed between VISIT 2 and VISIT 3 [but should be done at nearest point to VISIT 3])

- UFS-QOL
- Clinical laboratory tests
- Pharmacodynamic measurements
- Standard 12-lead ECG
- AE
- Concomitant medications
- Dispensing of study drugs for the Treatment
- Compliance of study drug administration
- PGx sample collection (perform only in subjects who consent to participate in PGx research [see Section 9.1.12])

9.3.2.2 VISIT 4 (Day 29)

The following procedures should be performed at VISIT 4:

- Pregnancy test (urine)
- Physical examination
- Vital signs and weight
- Patient diary (collected and distributed)
- Clinical laboratory tests
- Pharmacodynamic measurements
- AE
- Concomitant medications
- Dispensing of study drugs for the Treatment
- Compliance of study drug administration
- PGx sample collection (perform only in subjects who consent and from whom the sample has not been collected [see Section 9.1.12])

9.3.2.3 VISIT 5 (Day 57)

The following procedures should be performed at VISIT 5:

- Pregnancy test (urine)
- Physical examination
- Vital signs and weight
- Patient diary (collected and distributed)

- Clinical laboratory tests
- Pharmacodynamic measurements
- AE
- Concomitant medications
- Dispensing of study drugs for the Treatment
- Compliance of study drug administration
- PGx sample collection (perform only in subjects who consent and from whom the sample has not been collected [see Section 9.1.12])

9.3.3 Final Visit or Early Termination

9.3.3.1 VISIT 6 (Day 85) (or Early Termination)

The final visit during the treatment will be performed on VISIT 6 (85 days after the initial dose of the study medication for the Treatment). The following procedures should be performed. If early termination occurs during the Treatment, the same procedures scheduled at VISIT 6 should be performed.

- Pregnancy test (urine)
- Physical examination
- Vital signs and weight
- Patient diary (collected)
- Transvaginal ultrasound (see Section 9.1.16)
- UFS-QOL
- Clinical laboratory tests
- Pharmacodynamic measurements
- Standard 12-lead ECG
- AE
- Concomitant medications
- Compliance of study drug administration
- PGx sample collection (perform only in subjects who consent and from whom the sample has not been collected [see Section 9.1.12])

For all subjects receiving study medication, the investigator or subinvestigator must complete the Subject Status eCRF page.

9.3.4 Follow-up

9.3.4.1 VISIT 7 (Final visit of the Follow-up, 28 days after last dose)

The Follow-up lasts for 4 weeks (28 days) from the day after the final dose of study drug. The following procedures should be performed at the final visit of the Follow-up (VISIT 7). If early termination occurs during the Treatment, the same procedures scheduled at VISIT 7 should be performed 4 weeks (28 days) after the end of treatment. If study termination occurs during the Follow-up, the same procedures scheduled at VISIT 7 should be performed.

- Pregnancy test (urine)
- Physical examination
- Vital signs and weight
- Status of menstruation recovery
- Clinical laboratory tests
- Pharmacodynamic measurements
- Standard 12-lead ECG
- AE
- Concomitant medications
- PGx sample collection (perform only in subjects who consent and from whom the sample has not been collected [see Section 9.1.12])

9.3.5 Post Study Care

The study medication will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

If the recovery of the first post-treatment menstruation is not observed by the visit at the end of the Follow-up (VISIT 7), the subject will undergo further follow-up using possible means such as by telephone interview, until the recovery of the first post-treatment menstruation is observed.

9.4 Biological Sample Retention and Destruction

Samples of 5 mL whole blood collected for PGx will be stored frozen at [redacted] (See the attachment 1).

The collected samples will be retained at specimen storage agency up to 15 years after the completion of the study.

When subjects request disposal of a stored sample during the retention period or the sponsor discontinues the application aimed at obtaining approval from the Ministry of Health, Labour and Welfare, the site will ask [redacted] to destroy the sample via the sponsor according to the procedure. The [redacted] will destroy the sample in

accordance with the procedure, and notify the site and sponsor. However, any samples should not be destroyed if all the documents (including medical records) have been destroyed which could identify the subject and it is impossible to link the sample to the subject.

Even if the sample can be linked to the subject, when PGx investigation has been conducted, the remaining samples will be destroyed and the results of PGx investigation of anonymized subject will be retained by the sponsor.

The sponsor will build a management system required for protection of the subject's personal information, define standards for collecting store and destruction of samples, and prepare appropriate procedures.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with this treatment or study participation.

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

10.1.2 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator or subinvestigator for any reason.
- AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as an AE.

Diagnoses 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) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator or subinvestigator judges the change to be beyond the range of normal physiologic fluctuation) by the investigator or subinvestigator. 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 failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as AEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition after informed consent is signed, the worsening or complication should be recorded appropriately as an AE. Investigator or subinvestigator should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious or severe in nature, that is, investigator or subinvestigator should ensure that the AE term recorded captures the change in the condition from Baseline (eg, "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, investigator or subinvestigator should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after starting administration of the study medication, the worsening or complication should be recorded appropriately as a new AE. Investigator or subinvestigator should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigator or subinvestigator should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences changes in severity of an AE that are not related to starting or changing the study medication, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as 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 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 pharmacologic action, should NOT be recorded as an AE. The investigator or subinvestigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered AEs, but instead will be documented 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.

Worsening of the target disease:

- Worsening of expected conditions (measured by the primary efficacy and other endpoints) within the normal course will not be recorded as AEs.

10.1.3 SAEs

An SAE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study:

1. Results in DEATH.
2. Is LIFE THREATENING.

- The term "life threatening" refers to an event in which the subject was 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 were more severe.

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).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Acute liver failure
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizure (including convulsion and epilepsia)	Pulmonary fibrosis (including interstitial pneumonia)
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
Toxic epidermal necrolysis / Stevens-Johnson syndrome	Neuroleptic malignant syndrome / malignant hyperthermia
Hepatic necrosis	Spontaneous abortion / stillbirth and fetal death

10.1.4 AEs of Special Interest

An adverse event of special interest (treatment-emergent only, serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator or subinvestigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigator or subinvestigator as to how and when they should be reported to Takeda (see Section 10.2.1.3).

10.1.4.1 LFT Abnormalities

A nonclinical study in monkeys reported abnormal LFT results. A clinical study of an oral GnRH antagonist having the same structure as TAK-385 also reported increased ALT and AST, which were relevant to the study medication. Therefore, LFT abnormalities are handled as AESIs.

Section 9.1.8 describes how to handle LFT abnormalities.

When LFT abnormalities meet the criteria specified in Section 7.5, the investigator or subinvestigator must immediately discontinue study medication and perform follow-up.

10.1.5 Severity of AEs

The different categories of severity are characterized as follows:

Mild: The event is transient and easily tolerated by the subject.
Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.
Severe: The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of AEs to Study Medication(s)

The causality of each AE to study medication(s) 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 cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, 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 drugs and concurrent treatments.

10.1.7 Causality of AEs to Study Procedures

The causality of each AE to study procedures will be assessed.

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

10.1.8 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or investigator or subinvestigator. The start date of the AE is defined as follows:

AE	Definition of Onset
Sign, Symptom, disease (diagnosed)	The date when a subject or the investigator/subinvestigator first noticed the sign or symptom.
Asymptomatic disease	The date when the diagnosis was confirmed; even if the finding suggests that this is asymptomatic disease persisting for a long time with diagnosis being confirmed with examination/test results (but no information of the start date).
Complication or worsening of an AE that occurs prior to the first exposure to study drug	The date when a subject or the investigator/subinvestigator first noticed worsening of the sign or symptom.
Abnormal laboratory value which was within normal limit at screening	The date of an examination where clinically significant abnormality was detected.
Abnormal laboratory value which was out of normal limit at screening and then deteriorate	The date of an examination where apparent increase/decrease or elevation/reduction is observed based on the course of laboratory test result.

10.1.9 End Date

The stop date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died. If the outcome of recovered/resolved cannot be confirmed at the study end, it should be recorded as an ongoing AE.

10.1.10 Pattern of Adverse Event

Episodic AEs (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Taken with Study Treatment

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE, the AE that occurred before the study medication administration.
- Drug Interrupted – the dose was interrupted due to the particular AE and the dose was restarted at subsequent day.

10.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE.
- Recovering/Resolving – the intensity is lowered by one or more stages; the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE with the condition remaining “recovering/resolving”.
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining “Not recovered/not resolved”.
- Recovered/Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs which are considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject’s participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

Collection of AEs will commence from the time the subject signs the informed consent. Routine collection of AEs will continue until VISIT 7 (or early termination).

10.2.1.2 AE Reporting

At each study visit, the investigator or subinvestigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious AE that occurs prior to the first exposure to study drug must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious AEs that occur prior to the first exposure to study drug, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs that occur after the first exposure to study drug, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator or subinvestigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and end date.
3. Pattern.
4. Severity.
5. Investigator's opinion of the causality between the event and administration of study medication(s).
6. Investigator's opinion of the causality to study procedure(s), including the details of the suspected procedure.
7. Action taken with study treatment. (not applicable for the AE that occurred before the study medication administration)
8. Outcome of event.
9. Seriousness.
10. After administration of study drug
11. Treatment emergent

The patient diary and UFS-QOL will not be used as a primary means to collect AEs. However, should the investigator or subinvestigator become aware of a potential AE through the information collected with these instruments, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

10.2.1.3 AE of Special Interest Reporting

If this abnormality, which occurs during the Run-in, the treatment period or the follow-up period, is considered to be clinically significant based on the criteria below, it should be reported to the sponsor (described in the separate contact information list) immediately or within 1 business day of first onset or subject's notification of the event. An AESI name Form or an SAE Form should be completed, signed and/or sealed by the principal investigator, and reported to appropriate personnel in the separate contact information list within 10 business days.

- Laboratory value threshold if applicable.
- Premature termination for the AE of special interest, if applicable.
- Any other specific criteria.

Investigator shall refer to the "Checklist for Reporting Liver Function Test Abnormalities" (Appendix C), when writing the report.

The criterion for a LFT abnormality is:

- ALT or AST >3 × ULN

When a subject is noted to have ALT or AST >3 × ULN and total bilirubin >2 × ULN, the event should be handled as an SAE if the investigator concludes from the results of retesting (see Section 9.1.8 for procedures) that no factors, other than the study drugs, can account for it. The steps specified in Section 10.2.2 are followed to collect and report the event.

The AESIs have to be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

An SAE should be reported to the sponsor (described in the separate contact information list) within 1 business day of first onset or subject's notification of the event. The principal investigator should submit the completed SAE form within 10 calendar days. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's or subinvestigator's name.
- Name of the study medication(s)

- Causality assessment.

Any SAE spontaneously reported to the investigator or subinvestigator following the AE collection period should be reported to the sponsor if considered related to study participation.

10.2.3 Reporting of Abnormal LFTs

If a subject is noted to have ALT or AST elevated >3 ×ULN, the abnormality should be handled as an AESI (see Section 10.2.1.3). The investigator or subinvestigator should report the event to the sponsor, promptly conduct examinations and tests to obtain more information from the subject, and explore possible causes of the event other than the study drug (eg, acute Type A, B, C, or E viral hepatitis, other acute hepatic disorders, general medical history, or concurrent conditions). Follow-up laboratory tests as described in Section 9.1.8 must also be performed.

If a subject is noted to have ALT or AST >3 ×ULN and bilirubin (total bilirubin) >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator or subinvestigator must contact the sponsor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A, B, C or E or other acute liver disease or medical history/concurrent medical conditions.

If the abnormality meets the criteria listed in Section 7.5 (Liver function test abnormalities), the study drug should be discontinued immediately.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator or subinvestigator should complete a follow-up SAE form or provide other written documentation and fax it immediately. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, the investigators, IRBs and the head of the study site. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 CRFs

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

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate study collaborator in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The following data will not be recorded into the eCRFs:

1) Results of clinical laboratory tests conducted at the central laboratory
2) Results of pharmacodynamic tests

After the lock of the clinical study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator or subinvestigator with use of change and modification records of the eCRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, source worksheets, all original signed and dated informed consent forms, electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees.

The investigator and the head of the institution are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the institution should discuss how long and how to retain those documents 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.

In addition, the investigator and the head of the institution should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to unblinding of subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

In this study, three kinds of analysis sets are defined: full analysis set (FAS), per protocol set (PPS) and safety analysis set. The FAS, the main analysis set used for primary efficacy analysis, will be defined as "all subjects who were randomized and received at least one dose of the study drug." The definition of each analysis set will be described in the Handling Rules for Analysis Data.

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, consulting a medical expert as needed. If necessary, the Handling Rules for Analysis Data will be supplemented with new handling rules that were not discussed at the planning stage. The Handling Rules for Analysis Data must be finalized prior to database lock.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized overall and by treatment group using the randomized set.

13.1.3 Efficacy Analysis

(1) Primary endpoint and analytical methods

Primary endpoint

Proportion of subjects with a maximum NRS score of 1 or less during the 28 days before the final dose of study drug

Primary analysis

The following analyses will be performed based on the FAS:

The proportion of subjects with a maximum NRS score of 1 or less during the 28 days before the final dose of study drug will be summarized by treatment group. Comparison between the treatment groups will be performed using a Fisher's exact test.

Secondary analysis

An analysis similar to the above "Primary analysis" will be performed using the PPS to assess the robustness of the results (sensitivity analysis).

(2) Secondary endpoints and analytical methods

Secondary endpoints

- Proportion of subjects with a maximum NRS score of 0 during the 28 days before the final dose of study drug
- Mean NRS score during the 28 days before the final dose of study drug
- Number of days without pain symptoms (NRS = 0) during the 28 days before the final dose of study drug

Analytical methods

1. Proportion of subjects with a maximum NRS score of 0

The proportion of subjects with a maximum NRS score of 0 during the 28 days before the final dose of study drug will be summarized by treatment group.

2. Mean NRS score

The observed values and the changes from baseline will be summarized by treatment group for each visit using descriptive statistics.

3. Number of days without pain symptoms (NRS = 0)

The observed values and the changes from baseline will be summarized by treatment group for each visit using descriptive statistics.

(3) Additional efficacy endpoints

Additional endpoints

Proportion of days using analgesics during the 28 days before the final dose of study drug

Analytical methods

For the proportion of days using analgesics (during the 28 days before the initiation of study drug administration), summary statistics will be provided by treatment group.

(4) Methods of data transformation and handling of missing data

Details will be described in the SAP.

(5) Significance level and confidence coefficient

- Significance Level: 5% (two-sided test)
- Confidence coefficient: 95% (two-sided)

13.1.4 Pharmacodynamic Analysis

Additional endpoints

LH, FSH, E_2, and P (Week 4, 8, 12 and Follow-up)

13.1.5 Safety Analysis

The following analyses will be based on the safety analysis set.

(1) Secondary endpoint

Treatment-emergent adverse events

A TEAE is defined as an AE whose date of onset occurs on or after the start of study drugs for the Treatment.

TEAEs will be coded using the MedDRA dictionary. The frequency distribution will be provided using the system organ class (SOC) and the preferred term (PT) for each treatment group as follows:

- All TEAEs
- Drug-related TEAEs
- Intensity of TEAEs
- Intensity of drug-related TEAEs
- TEAEs leading to study drug discontinuation
- Serious TEAEs
- TEAEs over time

Laboratory test results, standard 12-lead ECGs, vital signs and weight

For continuous variables, the observed values and the changes from baseline will be summarized by treatment group for each visit using descriptive statistics. Case plots will also be presented for the observed values.

For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided for each treatment group.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

Justification of Sample size

Within the subjects who recorded maximum NRS score of ≥4 during 1 menstrual cycle just before the start of the Treatment drug administration in the TAK-385 phase 2 study in Japanese patients with uterine fibroids, the proportion of subjects with a maximum NRS score of 1 or less during the 28 days before the final dose of study drug was 14.7% (5/34) in placebo group and 75.9% (22/29) in TAK-385 40 mg group.

A sample size of 28 per group would give a power of >90% when a Fisher's exact test with a significance level of 5% (2-sided) is used for the comparison between TAK-385 40 mg group

and placebo group, under the assumption that "the proportion of subjects with a maximum NRS score of 1 or less during the 28 days before the final dose of study drug" is 20.0% for placebo group and 65.0% for TAK-385 40 mg group (SAS ver.9.2 Power procedure).

Based on the above, 28 subjects are considered sufficient for the number of evaluable subjects per group. Thirty two subjects are to be randomized to each group on the assumption that some subjects will be excluded from the analysis of the primary endpoint.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study 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 (contract research organization [CRO]) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator, subinvestigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator or subinvestigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible and an approval from IRB should be obtained.

The investigator or subinvestigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency[MHRA], the Pharmaceuticals and Medical Devices Agency of Japan[PMDA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study 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 the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix D. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB Approval

IRBs must be constituted according to the applicable local requirements. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB 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 notify site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

Regarding PGx investigation using collected and stored specimens, analysis will be carried out at the time when detail is determined. The sponsor will create a research protocol for PGx investigations and a research protocol will require prior approval of the company IRB in Japan.

15.2 Subject 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 describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that she is free to withdraw at any time without giving a reason and without prejudice to her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent form. The informed consent form must be approved by the IRB prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator or subinvestigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject determines she will participate in the study, then the informed consent form must be signed and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator or subinvestigator must also sign and date the informed consent form at the time of consent and prior to subject entering into the study.

Once signed, the original informed consent form will be stored in the investigator's site file. The investigator or subinvestigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

PGx research should be explained to the subject using "Informed Consent Form for PGx research of TAK-385" after explanation about the study using the informed consent form has been given. Specimens for PGx research should be collected from subjects who consented to participate in the study and PGx research.

The procedure specified in Section 9.4 should be followed when a subject requests disposal of her PGx samples.

15.3 Subject Confidentiality

The sponsor and designees 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 identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or

date of birth may be used to verify the subject and accuracy of the subject's unique 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 (eg, FDA, MHRA, PMDA), the sponsor's designated auditors, and the appropriate IRBs 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, subject 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 investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, the protocol or study results are the sole responsibility of the sponsor.

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

The investigator and subinvestigator need to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

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 ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

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 sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator and subinvestigator have questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

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2. Lefebvre G, Vilos G, Allaire C, et al. The management of uterine leiomyomas. J Obstet Gynaecol Can. 2003;25:396-418;quiz 419-22.