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

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- 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.
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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, Phase 3 Study to Evaluate the Efficacy and Safety of Oral TAK-385 40 mg compared with Leuprorelin in the Treatment of Uterine Fibroids

<Short Title>

A Phase 3 Study to Evaluate the Efficacy and Safety of TAK-385 40 mg compared with Leuprorelin in the Treatment of Uterine Fibroids

Sponsor:	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome, Chuo-ku, Osaka		
Study Identifier:	TAK-385/CCT-002		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	TAK-385		
Date:	24 November 2015		

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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, Phase 3 Study to Evaluate the Efficacy and Safety of Oral TAK-385 40 mg compared with Leuprorelin in the Treatment of Uterine Fibroids</td><td>IND No.:
Not Applicable</td><td>EudraCT No.:
Not Applicable</td></tr>
<tr><td>Study Identifier: TAK-385/CCT-002</td><td colspan="2">Phase: 3</td></tr>
<tr><td colspan="3">Study Design:
This is a phase 3, multicenter, randomized, double-blind, parallel-group, non-inferiority study to evaluate the efficacy and safety of TAK-385 administered orally in daily dosing 40 mg for 24 weeks, compared with leuprorelin injection (once/4 weeks, 1.88 mg or 3.75 mg subcutaneous [SC]/time) in premenopausal subjects ≥ 20 years of age with symptomatic uterine fibroids. The primary objective of this study is to evaluate the efficacy of TAK-385 40 mg administered orally once daily for 12 weeks.
Subjects must be diagnosed to have uterine fibroids as confirmed by transvaginal ultrasound or other methods, and have symptoms of menorrhagia.
The total number of subjects to be randomized under double-blind conditions is 288 (144 subjects each for the TAK-385 40 mg group or leuprorelin 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, including pictorial blood loss assessment chart (PBAC) scores and 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 and leuprorelin placebo) will be administered under single-blind conditions from the day of VISIT 2 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 3 to 10, subjects should try to visit the study site during the morning in a fasted state and before taking the TAK-385 tablet. Subjects will be randomized in a 1:1 ratio to either TAK-385 40 mg group or leuprorelin group at VISIT 3. Subjects will be administered study drug (TAK-385 40 mg + leuprorelin placebo or TAK-385 placebo + leuprorelin) in a double-dummy method from the day of VISIT 3 to the day before VISIT 10 (or until early termination) under double-blind conditions. The investigator or subinvestigator will decide the dosage of leuprorelin at VISIT 2 in accordance with the approved dosage and administration, considering the body weight and symptoms of the individual subject. The dosage of leuprorelin will not be changed throughout the Run-in and Treatment in each subject. TAK-385 (or TAK-385 placebo) will be administered daily as a single oral dose before breakfast. Leuprorelin (or leuprorelin placebo) will be administered SC (injection) once every 4 weeks.
This study consists of Screening of approximately 1 to 6 weeks, a Run-in period of 3 to 6 weeks, a Treatment period of 24 weeks, and a Follow-up period of 4 weeks. The total period of study participation is approximately 32 to 40 weeks. If the recovery of the first post-treatment menstruation is not observed by the visit at the end of the Follow-up(VISIT 11), 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, every 2 weeks for a month after the initiation of study drug administration (VISIT 3) under double-blind conditions, and monthly thereafter.</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 leuprorelin injection (once/4 weeks, 1.88 mg or 3.75 mg SC/time) in subjects with uterine fibroids.</td></tr>
</table>

Secondary Objectives:

The secondary objective of this study is to evaluate the efficacy and safety of TAK-385 40 mg administered orally once daily for 24 weeks, compared with leuprorelin injection (once/4 weeks, 1.88 mg or 3.75 mg SC/time) in subjects with uterine fibroids.

Subject Population: Subjects aged 20 years or older inclusive, with uterine fibroids

Planned Number of Subjects:	**Planned Number of Sites:**
The following number of subjects will be randomized: TAK-385 40 mg group : 144 subjects Leuprorelin group : 144 subjects Total : 288 subjects	Approximately 40 sites
Dose Levels: TAK-385 Dose: 40 mg or placebo Regimen: Administered once daily before breakfast Leuprorelin Dose: 1.88 mg, 3.75 mg or placebo Regimen: Administered once every 4 weeks	**Route of Administration:** TAK-385: Oral Leuprorelin: SC
Duration of Treatment: 24 weeks	**Study Length:** Screening, Run-in, Treatment (24 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 diagnosis of menorrhagia with a total PBAC score of ≥ 120 in 1 menstrual cycle just before VISIT 3.
12. 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 #12).

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 Run-in (VISIT 2).
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 a previous or current history of blood disorders (eg, thalassemia, sickle cells anemia, folic-acid deficiency, and coagulopathy), excluding (latent) iron-deficiency anemia.
5. The subject has a known history of severe hypersensitivity or severe allergy to sanitary goods.
6. The subject has lower abdominal pain due to irritable bowel syndrome or severe interstitial cystitis.
7. 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.
8. The subject has a previous or current history of pelvic inflammatory disease within the 8 weeks prior to VISIT 1.
9. 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).
10. The subject has a history of panhysterectomy or bilateral oophorectomy.
11. The subject has had markedly abnormal uterine bleeding or anovulatory bleeding, as determined by the investigator or subinvestigator.
12. The subject has a malignant tumor or a history of a malignant tumor within the 5 years prior to VISIT 1.
13. The subject has been treated with any of the following drugs (excluding drugs for external use and dietary supplements) within the 4 weeks prior to VISIT 2: anti-coagulant drugs, anti-platelet drugs, tranexamic acid, selective estrogen receptor modulators (SERMs), activated vitamin D preparations, other vitamin D preparations, calcitonin, ipriflavone, steroid hormones, vitamin K preparations, teriparatide, or denosumab.
14. 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).
15. The subject has been treated with a bisphosphonate preparation within the 24 weeks prior to VISIT 2.
16. The subject has a previous or current history of hypersensitivity or allergies to leuprorelin, synthetic GnRH, GnRH agonists or GnRH antagonists, or has a previous or current history of severe hypersensitivity or severe allergy to other drugs.
17. The subject has nondiagnosable abnormal genital bleeding.
18. 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.
19. The subject has a previous or current history of osteoporosis, osteopenia, or other metabolic bone diseases.
20. 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).

21. The subject is inappropriate for participation in this study based on standard 12-lead electrocardiogram (ECG) findings, as determined by the investigator or subinvestigator.
22. 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.
23. 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.
24. The subject has a previous or current history of drug abuse (defined as any illicit drug use) or alcohol abuse.
25. 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 total PBAC score of < 10 from Week 6 to 12

Secondary Endpoints

1) Efficacy:

- Proportion of subjects with a total PBAC score of < 10 (from Week 2 to 6, from Week 18 to 24, and for 6 weeks before the final dose of study drug)
- Myoma volumes (Week 2, 4, 8, 12 and 24)

  Note: Only the largest myoma among those measurable at VISIT 1 will be measured throughout the study.
- Uterine volumes (Week 2, 4, 8, 12 and 24)
- Hemoglobin (HGB) (Week 4, 8, 12, 16, 20, 24 and Follow-up)
- Numerical rating scale (NRS) score (from Week 6 to 12, from Week 2 to 6, from Week 18 to 24, and for 6 weeks before the final dose)
- Uterine fibroid symptom and quality of life (UFS-QOL) score (Week 4, 8, 12, 16, 20, 24 and Follow-up)

2) Safety:

- Adverse events (AEs), vital signs, weight, standard 12-lead ECG, clinical laboratory tests, bone mineral density (BMD), biochemical bone metabolism markers (serum N-telopeptide [NTELOP] and bone specific alkaline phosphatase [BAP])

Additional Endpoints

1) Efficacy:

- Hematocrit (HCT), serum iron (Fe), and serum ferritin (Week 4, 8, 12, 16, 20, 24 and Follow-up)
- Use of analgesic medications during the Treatment (from Week 6 to 12, from Week 2 to 6, from Week 18 to 24, and for 6 weeks before the final dose)
- Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH) (Week 2, 4, 8, 12 and 24)

2) Safety:

- Period from the last dose of study drug to return of menstrual cycles

3) Pharmacodynamic effects:

- Luteinizing hormone (LH), follicle stimulation hormone (FSH), estradiol (E2), and progesterone (P) (Week 2,

4, 8, 12, 16, 20, 24 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 total PBAC score of < 10 from Week 6 to 12 will be summarized by treatment group. The point estimate and 2-sided 95% confidence interval of the difference in the percentage will be calculated between TAK-385 40 mg group and leuprorelin group (TAK-385 40 mg group – leuprorelin group). In addition, non-inferiority test using Farrington and Manning method with a non-inferiority margin of 15% will be conducted for the comparison between TAK-385 40 mg group and leuprorelin group.

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:

In a clinical study of ulipristal acetate (already approved in Europe) compared with leuprorelin conducted overseas, the proportion of subjects with a total PBAC score of < 75 for 28 days before Week 13 was 89.1% in the TAP-144-SR (1M) 3.75 mg group, and the proportion of subjects with a total PBAC score of ≤ 2 for 28 days before Week 13 was 80.4%.

In TAK-385 phase 2 study in the treatment of uterine fibroids, the point estimate (and corresponding 2-sided 95% confidence interval) of the proportion of subjects with a total PBAC score of < 10 from Week 6 to 12 was 83.6% (71.2%, 92.2%) in the TAK-385 40 mg group.

Based on the results of the above 2 studies, the proportions of subjects with a total PBAC score of < 10 from Week 6 to 12 in both TAK-385 40 mg group and leuprorelin group are estimated to be 83.6%.

Under this assumption, a sample size of at least 129 subjects per group will provide ≥ 90% power to demonstrate non-inferiority at 1-sided 0.025 level of significance, using a non-inferiority margin of 15% (nQuery Advisor 6.01).

Based on the above, a sample size of 129 subjects per group (258 subjects in total) is planned as the number of evaluable subjects. Assuming that approximately 10% of subjects will not be evaluable for the primary endpoint, 144 subjects are to be randomized to each group, for a total of 288 subjects.

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
BAP	bone specific alkaline phosphatase
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
DXA	dual-energy x-ray absorptiometry
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
GLDH	glutamate dehydrogenase
GnRH	gonadotropin-releasing hormone
hCG	human chorionic gonadotropin
HCT	hematocrit
HDL	high density lipoprotein
HGB	hemoglobin
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
NTELOP	N-telopeptide
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
TBA	total bile acid
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
WPAI:GH	Work Productivity and Activity Impairment Questionnaire:General Health

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 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 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.

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 leuprorelin injection (once/4 weeks, 1.88 mg or 3.75 mg SC/time) in subjects with uterine fibroids.

5.1.2 Secondary Objectives

The secondary objective of this study is to evaluate the efficacy and safety of TAK-385 40 mg administered orally once daily for 24 weeks, compared with leuprorelin injection (once/4 weeks, 1.88 mg or 3.75 mg SC/time) in subjects 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 total PBAC score of < 10 from Week 6 to 12

5.2.2 Secondary Endpoints

1) Efficacy:

- Proportion of subjects with a total PBAC score of < 10 (from Week 2 to 6, from Week 18 to 24, and for 6 weeks before the final dose of study drug)
- Myoma volumes (Week 2, 4, 8, 12 and 24)

  Note: Only the largest myoma among those measurable at VISIT 1 will be measured throughout the study.
- Uterine volumes (Week 2, 4, 8, 12 and 24)
- Hemoglobin (HGB) (Week 4, 8, 12, 16, 20, 24 and Follow-up)
- Numerical Rating Scale (NRS) score (from Week 6 to 12, from Week 2 to 6, from Week 18 to 24, and for 6 weeks before the final dose)
- Uterine fibroid symptom and QOL (UFS-QOL) score (Week 4, 8, 12, 16, 20, 24 and Follow-up)

2) Safety:

- Adverse events (AEs), vital signs, weight, standard 12-lead electrocardiogram (ECG), clinical laboratory tests, BMD, biochemical bone metabolism markers (serum N-telopeptide [NTELOP] and bone specific alkaline phosphatase [BAP])

5.2.3 Additional Endpoints

1) Efficacy:

- Hematocrit (HCT), serum iron (Fe), and serum ferritin (Week 4, 8, 12, 16, 20, 24 and Follow-up)
- Use of analgesic medications during the Treatment (from Week 6 to 12, from Week 2 to 6, from Week 18 to 24, and for 6 weeks before the final dose)
- Work Productivity and Activity Impairment Questionnaire:General Health (WPAI:GH) (Week 2, 4, 8, 12 and 24)

2) Safety:

- Period from the last dose of study drug to return of menstrual cycles

3) Pharmacodynamic effects:

- LH, FSH, E_2 and P (Week 2, 4, 8, 12, 16, 20, 24 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, non-inferiority study to evaluate the efficacy and safety of TAK-385 compared with leuprorelin injection (once/4 weeks, 1.88 mg or 3.75 mg SC/time) in premenopausal subjects ≥ 20 years of age with symptomatic uterine fibroids. The primary objective is to evaluate the efficacy of TAK-385 40 mg administered orally once daily for 12 weeks. The secondary objective is to evaluate the efficacy and safety of TAK-385 40 mg administered orally once daily for 24 weeks. In addition, the pharmacodynamics of continuous oral administration of TAK-385 40 mg for 24 weeks is to be assessed.

Subjects must be diagnosed to have uterine fibroids as confirmed by transvaginal ultrasound or other methods, and have symptoms of menorrhagia (the total PBAC score of ≥ 120 for the entire menstrual cycle immediately before VISIT 3). The total number of subjects to be randomized under double-blind conditions is 288 (144 subjects each for the TAK-385 40 mg group or leuprorelin 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, including PBAC scores and pain symptoms (baseline PBAC score: the total PBAC 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 and leuprorelin placebo) will be administered under single-blind conditions from the day of VISIT 2 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 3 to 10, subjects will receive study drug (TAK-385 and leuprorelin placebo, or TAK-385 placebo and leuprorelin) in a double blind manner. Subjects should try to visit the study site during the morning in a fasted state and before taking the TAK-385 tablet.

The study consists of Screening of approximately 1 to 6 weeks, a Run-in period of 3 to 6 weeks, a Treatment period of 24 weeks, and a Follow-up period of 4 weeks. The total period of study participation is approximately 32 to 40 weeks. If the recovery of the first post-treatment menstruation is not observed by the visit at the end of the Follow-up (VISIT 11), 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, every 2 weeks for a month after the initiation of study drug administration (VISIT 3) under double-blind conditions, and monthly thereafter.

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 leuprorelin group. Study drug (TAK-385 40 mg + leuprorelin placebo or TAK-385 placebo + leuprorelin) will be administered in a double-dummy method from the day of VISIT 3 to the day before VISIT 10 (or until early termination) under double-blind conditions.

The investigator or subinvestigator will decide the dosage of leuprorelin at VISIT 2 in accordance with the approved dosage and administration, considering the body weight and symptoms of the individual subject. Leuprorelin (or leuprorelin placebo) should be administered SC (injection) once every 4 weeks using the same dose throughout the Run-in and Treatment.

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

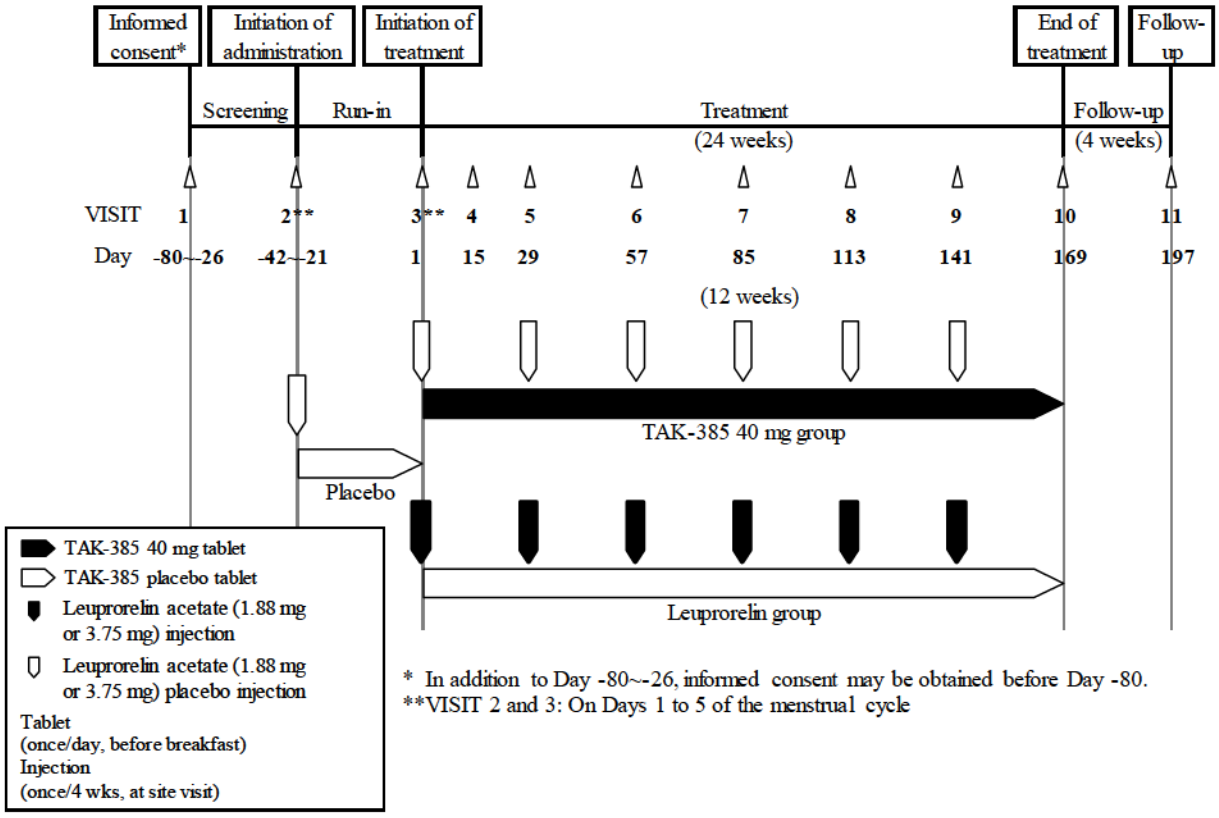

Figure 6.a Schematic of Study Design

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. Patients with menorrhagia have to frequently replace sanitary products. In addition, prolonged menorrhagia can induce iron-deficiency anemia. Therefore, menorrhagia is the main cause of QOL deterioration[1]. Surgery is performed for radical treatment of uterine fibroids. Drug therapy is used before surgery to alleviate anemia and to reduce the size of myoma[2, 3]. TAK-385 is thought to overcome the shortcomings of GnRH agonists commonly used in preoperative therapy. In this study, the improvement in the bleeding profile is examined for evaluation of improvement of QOL and efficacy of TAK-385 in patients with uterine fibroids.

The study is designed as a double-blind, parallel-group study to demonstrate the non-inferiority of TAK-385 compared with leuprorelin which is commonly used for the treatment of uterine fibroids. Since the period of general presurgical treatment for uterine fibroids is 3 months, which is stated to be a period for decreasing the size of myoma and improving anemia in some reports[3], the evaluation period of drug efficacy for the primary endpoint is to be set as 3 months. However, since medication for more than 3 months may sometimes be needed as a maintenance therapy, evaluation of drug efficacy and safety for up to 6 months are to be set as secondary endpoints. In benign indications GnRH agonist administration exceeding more than 6 months is generally not permitted because it may cause BMD loss resulting from a decrease in estrogen level.

The Treatment for this study is set at 6 months to evaluate the safety of TAK-385 and the potential effect of TAK-385 on BMD compared to GnRH agonists in subjects with uterine fibroids and menorrhagia. A single-blind treatment period (with placebo) is also included to investigate if there is any potential placebo effect on baseline blood loss and pain assessment. In addition, the Follow-up is included for safety assessment, including assessment of the recovery of menstruation after discontinuation of active treatment.

6.2.2 Justification for Dose Level and Regimen

1. TAK-385

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 and blood concentration of HGB. 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.

With regard to pharmacokinetics, [redacted] TAK-385 will be administered once daily before breakfast.

2. Leuprorelin

Leuprorelin is the first-line drug for the treatment of uterine fibroids. In the package insert, the "dosage and administration" section states the follows:

Usually, for adults, 1.88 mg of Leuprorelin Acetate is SC administered once every 4 weeks. However, for patients with heavy weight or those with markedly enlarged uterus, 3.75 mg is administered. The administration of this drug should be initiated on the first to fifth day after the start of menstrual period.

In this study, the dosage of leuprorelin (either 1.88 mg or 3.75 mg) is to be determined by the investigator or subinvestigator at VISIT 2 in accordance with the approved dosage and administration, considering the body weight and symptoms of the individual subject. Leuprorelin should be administered once every 4 weeks using the same dose throughout the Run-in and Treatment. Also, a double dummy is used to conduct this study under double blind conditions.

6.2.3 Justification for Endpoints

6.2.3.1 Primary Endpoint

Measuring menstrual blood loss is considered appropriate for the assessment of the bleeding profile in subjects with uterine fibroids having menorrhagia. In order to accurately assess the efficacy of TAK-385, the "proportion of subjects with a total PBAC score of < 10 from Week 6 to 12" is the primary endpoint. The evaluation period is set as 6 weeks, which is long enough to cover the subject's maximum menstrual cycle (38 days, which is the upper limit of normal [ULN] menstrual cycle).

The PBAC score was used for the measurement of menstrual blood loss in the Phase 2 Study, TAK-385/CCT-001, as overseas literature has reported its usefulness[4]. No collection of used sanitary products was necessary by using the PBAC score. In the result of TAK-385/CCT-001, the baseline values of PBAC score were higher in order of the subjects with submucosal fibroid, intramural fibroid, and subserosal fibroid, showing blood loss depends on the type of myoma. In addition, the correlation between the total PBAC score from Week 6 to 12 and the change in myoma and uterine volumes from baseline after Week 12 was relatively high. This result suggested that PBAC could be a tool for assessing the clinical symptoms of uterine fibroids. For these reasons, PBAC was considered an appropriate method for assessing the symptoms of uterine fibroids.

As the blood E_2 concentration decreases due to pharmacological effect after the administration of TAK-385, amenorrheic state is expected to be induced. However, the possibility of occurrence of metrorrhagia cannot be denied. Therefore, for the study TAK-385/CCT-001, the cut-off value of total PBAC score was set at 10 based on the cut-off value in other clinical studies and on the medical expert' s opinion. In order to assess the appropriateness of the cut-off value, the agreement between total PBAC score and the number of menstruations (0, ≥ 1) was assessed using the cut-off value of 2, 10, and 75, and as a result, the cut-off value of 10 produced the greatest κ coefficient. Therefore, the primary endpoint of this study was defined as the proportion of subjects with a total PBAC score of < 10 from Week 6 to 12.

6.2.3.2 Secondary Endpoints

A decrease in menstrual blood loss is to be assessed to demonstrate whether or not the decrease in menstrual blood loss can be maintained after administration for up to 6 months. Blood concentration of HGB is selected as a secondary endpoint as it is an important parameter of the bleeding profile, as described above. Myoma and uterine reduction prior to surgery is one of the most important goals of drug therapy. For this reason, myoma and uterine volumes are assessed using transvaginal ultrasound. Clinical symptoms unrelated to menorrhagia but associated with uterine fibroids, and also QOL are assessed using the NRS and UFS-QOL.

With regard to safety assessment, the hypoestrogenic state associated with long-term use of GnRH agonists has been reported to reduce BMD. For this reason, the effect of TAK-385 on BMD is to be assessed using dual-energy x-ray absorptiometry (DXA). In addition to the assessment of BMD, biochemical bone metabolism markers (serum NTELOP and BAP) are also to be assessed as a supplementary parameter of BMD. Other commonly used safety endpoints, such as AEs and vital signs, are also included.

6.2.3.3 Additional Endpoints

In addition to blood concentration of HGB, HCT and serum concentrations of Fe and ferritin are also measured for the assessment of anemia during the Treatment. As analgesics are permitted in this study under specific conditions, information on analgesic use is incorporated into the efficacy assessment. Also, WPAI:GH, validated questionnaire to measure impairments in work and activities[5], is used to evaluate the effects of TAK-385 on the QOL of patients with uterine fibroids.

Amenorrhea is induced due to the pharmacological effect of TAK-385. Therefore, in order to assess the time until menstruation returns after the end of treatment, the period from the last dose of study drug to return of menstrual cycles was selected as one of the other endpoints for additional assessment of the safety of TAK-385.

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 diagnosis of menorrhagia with a total PBAC score of ≥ 120 in 1 menstrual cycle just before VISIT 3.
12. 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 #12).

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 Run-in (VISIT 2).
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 a previous or current history of blood disorders (eg, thalassemia, sickle cells anemia, folic-acid deficiency, and coagulopathy), excluding (latent) iron-deficiency anemia.
5. The subject has a known history of severe hypersensitivity or severe allergy to sanitary goods.
6. The subject has lower abdominal pain due to irritable bowel syndrome or severe interstitial cystitis.
7. 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.
8. The subject has a previous or current history of pelvic inflammatory disease within the 8 weeks prior to VISIT 1.
9. 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.
10. The subject has a history of panhysterectomy or bilateral oophorectomy.

11. The subject has had markedly abnormal uterine bleeding or anovulatory bleeding, as determined by the investigator or subinvestigator.
12. The subject has a malignant tumor or a history of a malignant tumor within the 5 years prior to VISIT 1.
13. The subject has been treated with any of the following drugs (excluding drugs for external use and dietary supplements) within the 4 weeks prior to VISIT 2: anti-coagulant drugs, anti-platelet drugs, tranexamic acid, selective estrogen receptor modulators (SERMs), activated vitamin D preparations, other vitamin D preparations, calcitonin, ipriflavone, steroid hormones, vitamin K preparations, teriparatide, or denosumab.
14. 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).
15. The subject has been treated with a bisphosphonate preparation within the 24 weeks prior to VISIT 2.
16. The subject has a previous or current history of hypersensitivity or allergies to leuprorelin, synthetic GnRH, GnRH agonists or GnRH antagonists, or has a previous or current history of severe hypersensitivity or severe allergy to other drugs.
17. The subject has nondiagnosable abnormal genital bleeding.
18. 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.
19. The subject has a previous or current history of osteoporosis, osteopenia, or other metabolic bone diseases.
20. 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 $\geq$ 180 mmHg or diastolic blood pressure $\geq$ 110 mmHg at Screening and Run-in).
21. The subject is inappropriate for participation in this study based on standard 12-lead ECG findings, as determined by the investigator or subinvestigator.
22. 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.
23. 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.

24. The subject has a previous or current history of drug abuse (defined as any illicit drug use) or alcohol abuse.
25. 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 11 (or until early termination) to avoid confounding of the assessment of safety, efficacy and pharmacodynamics.

- Danazol
- GnRH analogues (except for leuprorelin provided by the sponsor for this study)
- 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 Anti-coagulants and Anti-platelets

Use of the following drugs (excluding drugs for external use and dietary supplements) is prohibited from VISIT 1 to 10 (or until early termination).

- Anti-coagulants (warfarin, heparin, anti-thrombin agent, urokinase, tisokinase, alteplase, nateplase, monteplase, nasaruplase)
- Anti-platelets (prostaglandin preparation, thromboxane synthetase inhibitor, ticlopidine hydrochloride, clopidogrel, cilostazol, sarpogrelate hydrochloride, ethyl icosapentate, beraprost sodium, dipyridamole, batroxobin)

7.3.1.3 Anti-anemic agents

Use of the following drugs (excluding drugs for external use and dietary supplements) is prohibited from VISIT 1 to 10 (or until early termination).

- Vitamin B12
- Vitamin B6
- Folic acid
- Iron preparations (injection)

7.3.1.4 Other Drugs That May Affect Efficacy, Safety, or Pharmacokinetics Assessment of TAK-385

Use of the following drugs (excluding drugs for external use and dietary supplements) is prohibited from VISIT 1 to 10 (or until early termination).

- Tranexamic acid
- 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
- Bisphosphonates
- Active and other vitamin D preparations
- Calcium preparations
- Calcitonins
- Ipriflavones
- Vitamin K preparations
- Teriparatide
- Denosumab

7.3.2 Drugs Permitted with Condition

7.3.2.1 Iron Preparations

An oral iron preparation is administered from VISIT 2 as specified below in subjects with blood HGB of < 10.0 g/dL at VISIT 1. Once started, the dose and regimen may not be changed up to VISIT 10 (or until early termination).

1) Dose and regimen of iron preparations: Iron 100 mg/day orally given

2) Criteria for use:

- HGB is < 10.0 g/dL: 100 mg/day
- HGB is ≥ 10.0 g/dL: Do not use

Only oral preparations may be used. No injection may be given.

Oral iron preparations are continued without changing the dose or regimen up to VISIT 10 (or until early termination) in patients who have been using them before entering into the study (prior to VISIT 1).

Regardless of with or without iron preparations administration, the subjects must be withdrawn immediately when their HGB concentrations at VISIT 2 or later decrease to < 8.0 g/dL.

Use of an iron preparation may be interrupted when an AE occurs due to its use or when the investigator or subinvestigator makes an overall decision that the subject no longer needs it based on anemia-related and other parameters.

7.3.2.2 Analgesics

Use of analgesics is **ONLY permitted under the following conditions** from VISIT 1 to 10 (or until early termination). This restriction was set because it is likely to have an impact on the evaluation of 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, use of intrauterine device (IUD), and transfusions are prohibited from VISIT 1 to VISIT 11 (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 (it is very important for the evaluation of TAK-385 in this study to keep a daily record of menstrual blood loss and entering information on the use of study drugs and analgesics).
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 TAK-385 tablet for the Run-in from the day of VISIT 2, and start taking the TAK-385 tablet for the Treatment from the day of VISIT 3. The subject should take the TAK-385 tablet every day as instructed by the investigator or subinvestigator. Taking the TAK-385 tablet every day is very important for the drug to show its expected effects.
11. The subject should take the TAK-385 tablet every day before breakfast during the Run-in and the Treatment, and should try to take the TAK-385 tablet at approximately the same time each day. If the subject forgets to take the TAK-385 tablet before breakfast, she should take it before lunch on the same day. If the subject forgets to take the TAK-385 tablet 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 10, follow the instructions below:

    <VISIT 2>

    The subject should try to visit the study site during the morning and undergo the designated study procedures as far as possible.

    <VISITS 3 and 10>

    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.

    <VISITS 4, 5, 6, 7, 8 and 9>

    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. On VISIT 2, 7 and 10 (or early termination), the subject should try to visit the study site at the same time and undergo the designated study procedures to the maximum extent possible.
13. The subject should always use the designated sanitary products provided by the study site during the study period (see section 9.1.16 for details on sanitary products). If it becomes difficult to continue to use the designated sanitary products during the study period, for reasons such as the onset of AEs, she should stop using the designated

sanitary products, report that fact to the investigator, subinvestigator, or study collaborator by telephone or other appropriate means, and ask for further instructions.

14. During the study period, the subject should always use the sanitary products provided by the study site, except in cases as stated in the instruction No.13. The subject must not use the sanitary products that the subject has been using before entering this study. The subject should avoid wearing the same product for long hours, except during sleeping hours, and change the product frequently so that the area in contact with the product is kept clean. Even during sleeping hours, the subject should try to avoid wearing the same product for more than 8 hours. Except during the menstruation period, the subject may use other sanitary products for preventing staining of underwear, but must switch to the sanitary product provided by the study site as soon as possible when bleeding is confirmed.
15. 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.
16. 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, etc.

- 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). If subject wishes to withdraw from the study to proceed to surgery, the category No.9 "Recovery leading to surgery" should be recorded.

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 menstrual blood loss after start of study drug administration) and judges continued participation in the study would pose an unacceptable risk to the subject.

9. Bone mineral density loss. The subjects with BMD measured by DXA at VISIT 7 is < 90% of baseline (or subjects with BMD changes from baseline > 10%), or the investigator or subinvestigator makes an overall risk-benefit assessment for the subject and decides to stop the study drug administration, even if the subject's BMD maintains ≥ 90% of baseline (or with a BMD change from baseline ≤ 10%).
10. Recovery leading to surgery. The subject who does not apply to any of the above category 1 to 8 and has a favorable outcome (eg, the improvement in the bleeding profile, the reduction in myoma and uterine volumes, and improvement in anemia) leading to the proceeding to surgery, and the investigator or subinvestigator judges that it is appropriate to proceed to surgery and not ethically desirable for the subject to be administered the study drug any longer.
11. Reduction of HGB concentration. Regardless of with or without iron preparations administration, HGB concentration of subject at VISIT 2 or later decreases to < 8.0 g/dL.
12. 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

1. TAK-385

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.

2. Leuprorelin

Study drug name: leuprorelin acetate

Nonproprietary name: leuprorelin (INN)

Chemical name:

5-Oxo-prolyl-histidyl-tryptophyl-seryl-tyrosyl-$_D$-leucyl-leucyl-arginyl-*N*-ethyl-prolinamide monoacetate

Dosage form and content:

Name	Content
Leuprorelin acetate 1.88 mg injection	Contains 1.88 mg of leuprorelin per vial
Leuprorelin acetate 3.75 mg injection	Contains 3.75 mg of leuprorelin per vial
Leuprorelin acetate 1.88 mg placebo injection	Contains no leuprorelin per vial
Leuprorelin acetate 3.75 mg placebo injection	Contains no leuprorelin per vial

Appearance: the powder for both of the leuprorelin acetate 1.88 mg injection and the corresponding placebo injection, and the powder for both of the leuprorelin acetate 3.75 mg injection and the corresponding placebo injection are indistinguishable in appearance from each other. The vials filled with them are also indistinguishable from each other.

3. Vehicle for suspension

An ampule (1 mL) contains water for injection, and 50 mg of D-mannitol, 5 mg of carmellose sodium, and 1 mg of polysorbate 80 as excipients.

8.1.1.2 Packaging and Labeling

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

1) TAK-385

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) Leuprorelin

One vial of leuprorelin acetate 1.88 mg placebo injection or leuprorelin acetate 3.75 mg placebo injection and an ampule of vehicle for suspension (for one injection) are contained in a small box. One small box is allocated to each subject.

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

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

1) TAK-385

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. Six 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.

2) Leuprorelin

One vial of leuprorelin acetate (1.88 mg, 3.75 mg, 1.88 mg placebo, or 3.75 mg placebo) injection and an ampule of vehicle for suspension (for one injection) are contained in a small box. One vial of leuprorelin acetate (1.88 mg, 3.75 mg, 1.88 mg placebo, or 3.75 mg placebo) injection and 3 ampules of vehicle for suspension are contained in a small box as a spare. Eight

small boxes (6 boxes for scheduled once-use and 2 boxes for spare use) are placed in an outer case. One outer case is allocated to each subject. All packaging materials for leuprorelin 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

All investigational drugs 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 drugs must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Investigational drugs must be stored under the conditions specified on the label, and remain in the original container until dispensed. Leuprorelin acetate (1.88 mg or 3.75 mg) injection, leuprorelin acetate (1.88 mg or 3.75 mg) placebo injection and their vehicle for suspension are to be kept in the original containers until use.

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 • One leuprorelin acetate (1.88 mg or 3.75 mg) placebo injection once/4 weeks
Treatment	TAK-385 40 mg group	• One TAK-385 40 mg tablet per day • One leuprorelin acetate (1.88 mg or 3.75 mg) placebo injection once/4 weeks
	Leuprorelin group	• One TAK-385 placebo tablet per day • One leuprorelin acetate (1.88 mg or 3.75 mg) injection once/4 weeks

1. TAK-385

1) Run-in

Administration of TAK-385 placebo tablets should be started on the day of VISIT 2. 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 10, 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, 5, 6, 7, 8 or 9, 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).

2. Leuprorelin

1) Run-in

The investigator or subinvestigator will decide the dosage of leuprorelin acetate (1.88 mg or 3.75 mg) injection for individual subjects at VISIT 2 (see Section6.1.2 for details). Leuprorelin acetate (1.88 mg or 3.75 mg) placebo injection should be administered SC on the day of VISIT 2.

2) Treatment

Leuprorelin acetate (1.88 mg, 3.75 mg, 1.88 mg placebo, or 3.75 mg placebo) injection are administered SC once every 4 weeks on the day of visiting the study sites. At VISIT 4, leuprorelin acetate (1.88 mg, 3.75 mg, 1.88 mg placebo, or 3.75 mg placebo) injection should NOT be administered.

For dosing, powder in a vial should be sufficiently suspended with the vehicle for suspension (1 mL). A needle for injection of 23 Gauge or larger should be used. For optimal SC injection, need to follow the following instructions.

- The site for SC injection should be the brachial, abdominal or gluteal region.
- The injection site should be changed each time. Repeated injection should not be given at the same site.
- Confirmation should be made to see that the needle is not piercing a blood vessel.
- The patients should be instructed not to massage the injection site.

Instructions for preparing method of leuprorelin acetate (1.88 mg or 3.75 mg) injection and leuprorelin acetate (1.88 mg or 3.75 mg) placebo injections are as follows.

- The injectable solution should be prepared at the time of use and be used immediately after preparing the suspension.
- If any sedimentation is noticed in the suspension of vial product, such suspension should be used after swirling the vial gently, avoiding formation of bubbles, to resuspend the particles uniformly.

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 drugs 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

At VISIT 2, the investigator or subinvestigator will decide the dosage of leuprorelin acetate (1.88 mg or 3.75 mg) injection for individual subjects (see Section 6.1.2 for details). The investigator or his/her designee checks each subject's eligibility for the Treatment at VISIT 3, and register via website the subject on registration/randomization center of the subject's qualification for randomization to the treatment groups (a unique number designating each study drug [TAK-385 tablet and leuprorelin acetate injection] for 1 subject is issued). When the subject registration/randomization center shows drug numbers, 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. The subject will be registered at subject registration/randomization center even if the subject is ineligible for randomization.

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 leuprorelin 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 VISIT 2 and 3, all subjects will receive the placebo treatment (TAK-385 placebo tablets and leuprorelin acetate [1.88 mg or 3.75 mg] placebo injection) 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, leuprorelin acetate [1.88 mg or 3.75 mg] placebo injection for the Run-in, TAK-385 40 mg tablet or TAK-385 placebo tablet, leuprorelin acetate [1.88 mg or 3.75 mg] injection, and leuprorelin acetate [1.88 mg or 3.75 mg] placebo injection 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 11 [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 23 mL (including PGx sample collection), and the approximate total volume of blood for the study is 170 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 (a) HCT (a) 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 Triglycerides Glucose HGB A1C Creatinine Blood urea nitrogen (BUN) Creatine kinase Urate Sodium Potassium Chloride Calcium Phosphate Magnesium Ferritin (a) Fe (a) Bile acid (total bile acid [TBA]) Glutamate dehydrogenase (GLDH)	Qualitative (protein, glucose, occult blood, urobilinogen, bilirubin) Pregnancy test (human chorionic gonadotropin [hCG])
Hormone	**Biochemical bone metabolism markers**	
LH FSH E_2 P	NTELOP BAP	

(a) Anemia-related measurement (see Section 9.1.18)

The central laboratory (see the attachment 1) will perform laboratory tests for hematology, chemistries, urinalysis (excluding pregnancy tests), hormone, biochemical bone metabolism markers.

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 11 (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 11 (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 PBAC

The volume of menstrual blood loss is measured using the PBAC 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 10 (or until early termination).

From VISIT 1, subjects are required to use only the sanitary products designated by the sponsor. The products supplied by the study site are shown below:

- Sanitary towel (pad): [redacted]
- Tampon: [redacted]

Products other than those supplied by the study site may only be used outside the menstruation period to prevent staining of the underwear. However, those sanitary products supplied by the study site must be immediately used when bleeding is observed.

Subjects should check the sanitary product after use, and record the number of used products that look similar to each of the diagrams of the sanitary towel or tampon in the PBAC sheet every day.

The investigator or subinvestigator should check the recorded PBAC scores at each subject's visit. Additionally, the start/end date of menstruation must be recorded in CRF in reference to the PBAC score. 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 an change history that captures the old information, the new information, identification of the person making the correction and the date 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 a change history that captures the old information, the new information, identification of the person making the correction and the date of the correction.

Three diagrams each for the sanitary towel and tampon are shown in the PBAC score sheet. Each diagram represents a lightly stained, moderately stained, or completely saturated pad or tampon. The following scores are assigned to these categories:

- Add 1, 5, or 20 points for each lightly stained, moderately stained, or completely saturated pad, respectively.
- Add 1, 5, or 10 points for each lightly stained, moderately stained, or completely saturated tampon, respectively.
- Add 1 or 5 points for each blood clot of smaller than 1 cm or for each blood clot of 1 cm or larger in the longest diameter, respectively.
- Add 5 points for each episode of flooding.

A total PBAC score is calculated by summing the points for the number of used sanitary towels and used tampons, the number of blood clots, and the number of flooding per designated period.

9.1.17 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.

9.1.18 Anemia-related Measurements

Anemia-related measurements consist of HGB, HCT, Fe, and ferritin concentrations. These are determined at the central laboratory (see the attachment 1).

9.1.19 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 10 (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. 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.

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, 5, 6, 7, 8, 9, 10 and 11 and has subjects fill it out before physical examination at site visit.

9.1.20 WPAI:GH

WPAI:GH (see Appendix C) is a questionnaire about the past 7 days to measure the effects of health in general and specific symptoms on work productivity and outside of work consisting of 6 questions. WPAI:GH should be assessed before physical examination at site visit. At the visit that UFS-QOL is scheduled, WPAI:GH should be assessed after UFS-QOL assessment.

9.1.21 Status of Menstruation Recovery

If the first menstruation after the end of study drug administration is observed before the VISIT 11 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 11 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.

9.1.22 BMD

BMD is determined using DXA. Throughout the study, the same apparatus is used and operated in the same scan mode for all scans for an individual subject. The investigator or subinvestigator records the date of each scan and the following results of the scan in the eCRF:

Measurement Site: 2nd to 4th lumbar vertebrae (L2 to L4)

Parameters: mean BMD (g/cm^2) of L2 to L4, and T-score (standard deviations from a young, sex-specific reference mean BMD) of L2 to L4

9.1.23 Biochemical Bone Metabolism Markers

Biochemical bone metabolism markers are determined at the contract laboratory organization at the time points specified in the "Schedule of Study Procedures" (Appendix A). Blood is drawn roughly at the same time each day (as far as possible) in each subject.

Venous blood is collected into the container distributed to the study sites. Serum is placed into the tubes that are also distributed to the sites. The samples are kept frozen at or below -20°C until analysis.

Parameters: Serum NTELOP and BAP

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 following information in the eCRF.

Run-in period

- TAK-385 placebo: the start/end date of dosing
- Leuprorelin placebo: the date of dosing

Treatment period

- TAK-385 blinded: the start/end date of dose, and the date of non-dosing
- Leuprorelin blinded: the date of dosing

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.

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 9.1.17. 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])
- Anemia-related measurements
- Clinical laboratory tests
- Standard 12-lead ECG
- AE
- Concomitant medications

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. 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. Study drugs for the Run-in are started in a single-blind fashion on the day of VISIT 2. If a dose is missed before breakfast, subjects may take the drug before lunch on the

same day. If a dose is missed before breakfast and lunch, subjects may take the drug before dinner on the same day.

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)
- BMD (perform between VISIT 2 and VISIT 3 so that the results can be reviewed at VISIT 3)
- Anemia-related measurements
- Clinical laboratory tests
- Biochemical bone metabolism markers
- AE
- Concomitant medications
- Deciding the dosage of leuprorelin
- Dispensing of study drugs for the Run-in

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 menstration after VISIT 1, without taking the TAK-385 tablet 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 9.1.17. 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])
- BMD (perform between VISIT 2 and VISIT 3 so that the results can be reviewed at VISIT 3)
- UFS-QOL
- WPAI:GH
- Anemia-related measurements
- 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 15)

The following procedures should be performed at VISIT 4:

- Pregnancy test (urine)
- Physical examination
- Patient diary (collected and distributed)
- Transvaginal ultrasound (see Section 9.1.17)
- WPAI:GH
- Clinical laboratory test (only TBA and GLDH are assessed)
- Pharmacodynamic measurements
- 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])

9.3.2.3 VISIT 5 (Day 29)

The following procedures should be performed at VISIT 5:

- Pregnancy test (urine)
- Physical examination
- Vital signs and weight
- Patient diary (collected and distributed)
- Transvaginal ultrasound (see Section 9.1.17)
- UFS-QOL
- WPAI:GH
- Anemia-related measurements
- 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])

9.3.2.4 VISIT 6 (Day 57)

The following procedures should be performed at VISIT 6:

- Pregnancy test (urine)
- Physical examination
- Vital signs and weight
- Patient diary (collected and distributed)
- Transvaginal ultrasound (see Section 9.1.17)
- UFS-QOL
- WPAI:GH
- Anemia-related measurements

- 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])

9.3.2.5 VISIT 7 (Day 85)

The following procedures should be performed at VISIT 7:

- Pregnancy test (urine)
- Physical examination
- Vital signs and weight
- Patient diary (collected and distributed)
- Transvaginal ultrasound (see Section 9.1.17).
- BMD
- UFS-QOL
- WPAI:GH
- Anemia-related measurements
- Clinical laboratory tests
- Pharmacodynamic measurements
- Biochemical bone metabolism markers
- 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])

9.3.2.6 VISIT 8 and 9 (Day 113 and 141)

The following procedures should be performed at VISIT 8 and 9:

- Pregnancy test (urine)
- Physical examination
- Vital signs and weight
- Patient diary (collected and distributed)
- UFS-QOL
- Anemia-related measurements
- 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 10 (Day 169) (or Early Termination)

The final visit during the Treatment will be performed on VISIT 10 (169 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 10 should be performed.

- Pregnancy test (urine)
- Physical examination
- Vital signs and weight
- Patient diary (collected)
- Transvaginal ultrasound (see Section 9.1.17).
- BMD
- UFS-QOL
- WPAI:GH
- Anemia-related measurements
- Clinical laboratory tests

- Pharmacodynamic measurements
- Biochemical bone metabolism markers
- 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 11 (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 11). If early termination occurs during the Treatment, the same procedures scheduled at VISIT 11 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 11 should be performed.

- Pregnancy test (urine)
- Physical examination
- Vital sign and weight
- Status of menstruation recovery
- UFS-QOL
- Anemia-related measurement
- Clinical laboratory test
- Pharmacodynamic measurement
- 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 11), 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 investigators 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 occured 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 11 (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 occured before the study medication administration)
8. Outcome of event.
9. Seriousness.
10. After administration of study drug
11. Treatment emergent

The patient diary, UFS-QOL and WPAI:GH 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 D), 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 total PBAC score of < 10 from Week 6 to 12

Primary analysis

The following analyses will be performed based on the FAS:

The proportion of subjects with a total PBAC score of < 10 from Week 6 to 12 will be summarized by treatment group. The point estimate and 2-sided 95% confidence interval of the difference in the percentage will be calculated between TAK-385 40 mg group and leuprorelin group (TAK-385 40 mg group – leuprorelin group). In addition, non-inferiority test using Farrington and Manning method with a non-inferiority margin of 15% will be conducted for the comparison between TAK-385 40 mg group and leuprorelin group.

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 total PBAC score of < 10 (from Week 2 to 6, from Week 18 to 24, and for 6 weeks before the final dose of study drug)
- Myoma volumes (Week 2, 4, 8, 12 and 24)
- Uterine volumes (Week 2, 4, 8, 12 and 24)
- HGB (Week 4, 8, 12, 16, 20, 24 and Follow-up)
- NRS score (from Week 6 to 12, from Week 2 to 6, from Week 18 to 24, and for 6 weeks before the final dose)
- UFS-QOL score (Week 4, 8, 12, 16, 20, 24 and Follow-up)

Analytical methods

1. Proportion of subjects with a total PBAC score of < 10

Frequency will be summarized by treatment group. The point estimate and 2-sided 95% confidence interval of the difference in the percentage will be calculated between TAK-385 40 mg group and leuprorelin group.

2. Myoma and uterine volumes, HGB, NRS score and UFS-QOL scores

For each variable, summary statistics will be provided by treatment group for each visit. Two-sided 95% confidence interval of the difference will be calculated between TAK-385 40 mg and leuprorelin group.

(3) Additional efficacy endpoints

Additional endpoints

- HCT, serum Fe, and serum ferritin (Week 4, 8, 12, 16, 20, 24 and Follow-up)
- Use of analgesic medications during the Treatment (from Week 6 to 12, from Week 2 to 6, from Week 18 to 24, and for 6 weeks before the final dose)
- WPAI:GH during the Treatment (Week 2, 4, 8, 12 and 24)

(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: 2.5% (one-sided, non-inferiority test)

Confidence coefficient: 95% (two-sided)

13.1.4 Pharmacodynamic Analysis

Additional endpoints

LH, FSH, E_2, and P (Week 2, 4, 8, 12, 16, 20, 24 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, weight, BMD and biochemical bone metabolism markers (serum NTELOP and BAP)

For continuous variables except BMD, the observed values and the changes from baseline will be summarized by treatment group for each visit using descriptive statistics. For BMD, the observed values and the percent 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.

(2) Additional endpoint

- Period from the last dose of study drug to return of menstrual cycles.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

Justification of Sample size

In a clinical study of ulipristal acetate (already approved in Europe) compared with leuprorelin conducted overseas, the proportion of subjects with a total PBAC score of < 75 for 28 days before Week 13 was 89.1% in the TAP-144-SR (1M) 3.75 mg group, and the proportion of subjects with a total PBAC score of ≤ 2 for 28 days before Week 13 was 80.4%.

In TAK-385 phase 2 study in the treatment of uterine fibroids, the point estimate (and corresponding 2-sided 95% confidence interval) of the proportion of subjects with a total PBAC score of < 10 from Week 6 to 12 was 83.6% (71.2%, 92.2%) in the TAK-385 40 mg group.

Based on the results of the above 2 studies, the proportions of subjects with a total PBAC score of < 10 from Week 6 to 12 in both TAK-385 40 mg group and leuprorelin group are estimated to be 83.6%.

Under this assumption, a sample size of at least 129 subjects per group will provide ≥ 90% power to demonstrate non-inferiority at 1-sided 0.025 level of significance, using a non-inferiority margin of 15% (nQuery Advisor 6.01).

Based on the above, a sample size of 129 subjects per group (258 subjects in total) is planned as the number of evaluable subjects. Assuming that approximately 10% of subjects will not be evaluable for the primary endpoint, 144 subjects are to be randomized to each group, for a total of 288 subjects.

Justification of non-inferiority margin

As the result of the TAK-385 phase 2 study in the treatment of uterine fibroids, the point estimate (and corresponding 2-sided 95% confidence interval) of the difference in the proportion of subjects with a total PBAC score of < 10 from Week 6 to 12 was 83.6% (73.9%, 93.4%) between the TAK-385 40 mg group and Placebo group. Assuming that leuprorelin has comparable effect to TAK-385 40 mg, the non-inferiority margin of 15% is considered smaller than the smallest effect size that leuprorelin would be reliably expected to have.

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 E. 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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