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

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

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

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

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-385/CCT-002

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

PHASE 3

Version**:** Final

Date**:** 1 AUG 2017

Prepared by:

[redacted]

[redacted]

Based on:

Protocol Version: Original

Protocol Date: 24 November 2015

1.1 Approval Signatures

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

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT FIGURES

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
PTE	Pretreatment event
QOL	quality of life
Run-in AE	run-in adverse event
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 OBJECTIVES

4.1 Primary Objectives

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 subcutaneously [SC]/time) in subjects with uterine fibroids.

4.2 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.

4.3 Additional Objectives

An additional objective of this study is to evaluate the pharmacodynamic effect, which is blood concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E_2), and progesterone (P).

4.4 Study Design

An overview of the study design is shown in Figure 4

4.4.1 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 pictorial blood loss assessment chart [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.

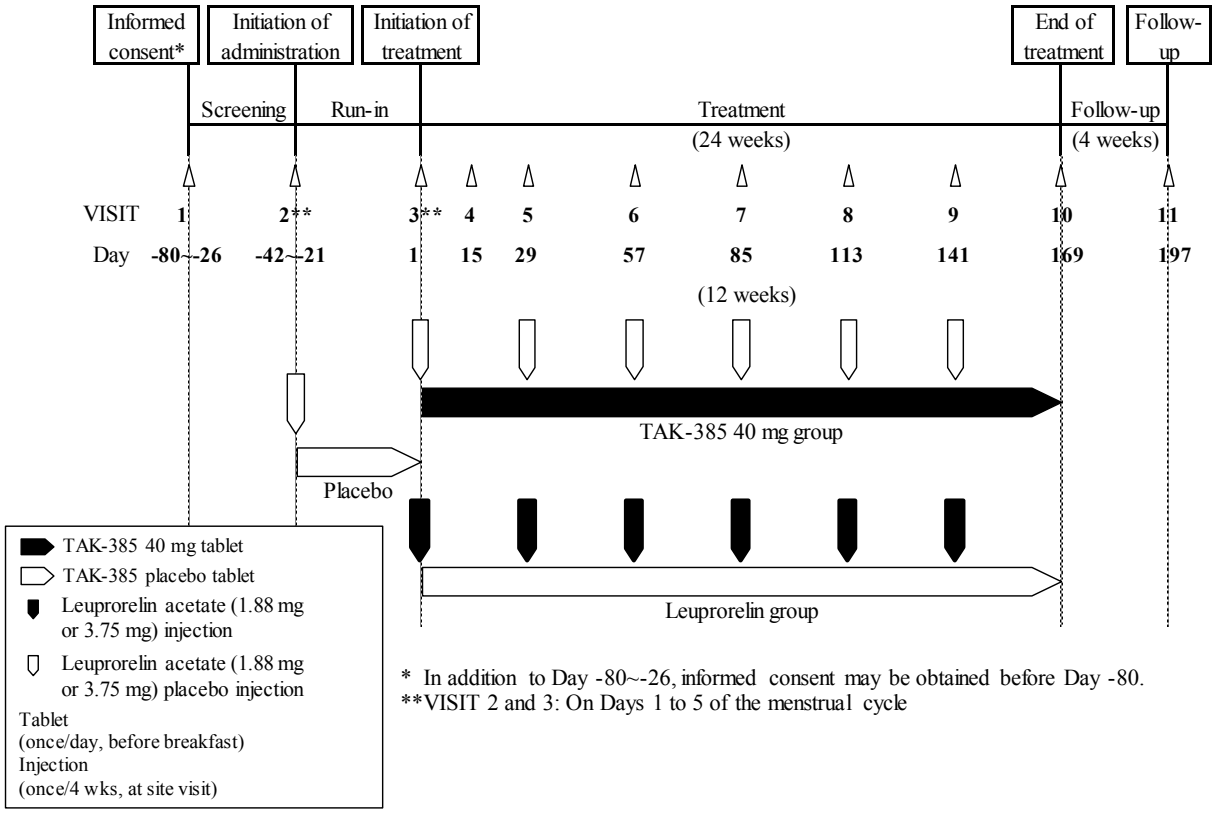
4.4.2 Dose Level and Regimen

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 4 Schematic of Study Design



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

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

1) Efficacy:

Proportion of subjects with a total PBAC score of < 10 from Week 6 to 12

5.2 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, bone mineral density (BMD), biochemical bone metabolism markers (serum N-telopeptide [NTELOP] and bone specific alkaline phosphatase [BAP])

5.3 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 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.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All statistical analyses will be conducted using SAS® Version 9.2, or higher.

A statistical test for the primary endpoint will be reported as 1-sided and will be assessed at α=0.025 significance level and all confidence intervals will be reported as 2-sided unless otherwise stated. P-values will be rounded to 4 decimal places prior to assessment of statistical significance.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the count and proportions of each possible value will be tabulated by treatment group. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated. Confidence intervals for continuous variables will be calculated based on t-statistics and ones for categorical variables will be based on Wald confidence intervals without using any model, unless otherwise stated.

7.1.1 Study Definitions

Duration of exposure to double-blind study drug (days) :

Date of last dose of double-blind study drug - date of first dose of double-blind study drug + 1

Double-blind study drug compliance (%) :

Number of TAK-385 blinded drugs taken/duration of exposure to TAK-385 blinded drug * 100 (rounded to 1 decimal places)

Disease duration (years):

((year of informed consent*12 + month of informed consent) –(year of first defined diagnosis of uterine fibroids*12 + month of first defined diagnosis of uterine fibroids))/12 (rounded to 1 decimal places)

Maximum drug holidays (days):

Maximum number of consecutive days on which the subject does not take the TAK-385 blinded drug for the treatment period

Total PBAC score from Week 6 to 12

Total PBAC score from Day 43 to earlier of Day 84 or Follow-up Day 3.
Similarly, Total PBAC score from Week 2 to 6 and from Week 18 to 24 will be defined as

those from Day 15 to earlier of Day 42 or Follow-up Day 3 and from Day 127 to earlier of Day 168 or Follow-up Day 3, respectively.

Total PBAC score for 6 weeks before the final dose of study drug
Total PBAC score for the last 42 days of the treatment

NRS score from Week 6 to 12
Average NRS score from Day 43 to earlier of Day 84 or Follow-up Day 3.
Similarly, NRS score from Week 2 to 6 and from Week 18 to 24 will be defined as average NRS score from Day 15 to earlier of Day 42 or Follow-up Day 3 and from Day 127 to earlier of Day 168 or Follow-up Day 3, respectively.

NRS score for 6 weeks before the final dose
Average NRS score for the last 42 days of the treatment

Total PBAC at baseline
Total PBAC score from first day of menstrual period confirmed at Visit 2 to a day prior to menstrual period confirmed at Visit 3

NRS score at baseline
Average NRS score from first day of menstrual period confirmed at Visit 2 to a day prior to menstrual period confirmed at Visit 3

Use of analgesic medications during the treatment from Week 6 to 12
((number of days with analgesic medications use between Day 43 and earlier of Day 84 or Follow-up Day 3)/(number of days with available data between Day 43 and earlier of Day 84 or Follow-up Day 3))*100 (rounded to 1 decimal places)
Similarly, use of analgesic medications during the treatment from Week 2 to 6 and from Week 18 to 24 will be defined as proportion of days with analgesic use between Day 15 and earlier of Day 42 or Follow-up Day 3 and between Day 127 and earlier of Day 168 or Follow-up Day 3, respectively.

Use of analgesic medications during the Treatment for 6 weeks before the final dose
((number of days with analgesic medications use for the last 42 days of the treatment)/(number of days with available data for the last 42 days of the treatment))*100 (rounded to 1 decimal places)

Proportion of subjects with a total PBAC score of < 10 from Week 6 to 12:
((number of subjects with a total PBAC score of less than 10 from Week 6 to 12)/(number of subjects with available PBAC score from Week 6 to 12))*100 (rounded to 1 decimal places)

Myoma volumes
D1*D2*D3*π/6 (cm^3)
Uterine volumes will be similarly calculated.
Definitions of D1, D2 and D3 are shown in protocol.

Duration of Menstruation Recovery
Date of menstruation recovery - date of last dose of double-blind study drug

Oral iron preparation

The drug with the following drug code of WHODD:
00023503001, 00023505001, 00023520001, 00023550009, 00023550074, 90059601001

7.1.2 Definition of Study Days

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

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

7.1.3 Definition of Study Visit Windows

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

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Day to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day, the later observation will be used.

Transvaginal ultrasound and WPAI

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-80 - 1	
Week 2	Study Day: 15	2 - 22	< 4
Week 4	Study Day: 29	23 - 43	< 4
Week 8	Study Day: 57	44 - 71	< 4
Week 12	Study Day: 85	72 - 127	< 4
Week 24	Study Day: 169	128 – 183	< 4

Anemia-related measurements (Hemoglobin [HGB], Hematocrit [HCT], Serum Fe, and Serum Ferritin) and UFS-QOL score

Visit	Scheduled Study Day	Time Interval (days)

	(days)	Study Day	Follow-up Day
Baseline	Study Day: 1	-80 - 1	
Week 4	Study Day: 29	2 – 43	< 4
Week 8	Study Day: 57	44 – 71	< 4
Week 12	Study Day: 85	72 – 99	< 4
Week 16	Study Day: 113	100 – 127	< 4
Week 20	Study Day: 141	128 – 155	< 4
Week 24	Study Day: 169	156 – 183	< 4
Follow-up	Follow-up Day: 28	2 <=	4 – 42

Clinical laboratory tests (except bile acid (total bile acid [TBA]) and glutamate dehydrogenase (GLDH)) and vital sign and weight

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-80 - 1	
Week 4	Study Day: 29	2 – 43	< 15
Week 8	Study Day: 57	44 – 71	< 15
Week 12	Study Day: 85	72 – 99	< 15
Week 16	Study Day: 113	100 – 127	< 15
Week 20	Study Day: 141	128 – 155	< 15
Week 24	Study Day: 169	156 – 183	< 15
Follow-up	Follow-up Day: 28	2 <=	15 – 42

Pharmacodynamic measurements

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-80 - 1	
Week 2	Study Day: 15	2 – 22	< 4
Week 4	Study Day: 29	23 – 43	< 4
Week 8	Study Day: 57	44 – 71	< 4
Week 12	Study Day: 85	72 – 99	< 4
Week 16	Study Day: 113	100 – 127	< 4

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Week 20	Study Day: 141	128 – 155	< 4
Week 24	Study Day: 169	156 – 183	< 4
Follow-up	Follow-up Day: 28	2 <=	4 – 42

Clinical laboratory tests (TBA and GLDH)

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-80 - 1	
Week 2	Study Day: 15	2 – 22	< 15
Week 4	Study Day: 29	23 – 43	< 15
Week 8	Study Day: 57	44 – 71	< 15
Week 12	Study Day: 85	72 – 99	< 15
Week 16	Study Day: 113	100 – 127	< 15
Week 20	Study Day: 141	128 – 155	< 15
Week 24	Study Day: 169	156 – 183	< 15
Follow-up	Follow-up Day: 28	2 <=	15 – 42

12-lead ECG

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-80 - 1	
Week 24	Study Day: 169	2 – 183	< 15
Follow-up	Follow-up Day: 28	2 <=	15 – 42

Biochemical bone metabolism markers and BMD

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-80 - 1	

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Week 12	Study Day: 85	2 – 127	< 15
Week 24	Study Day: 169	128 – 183	< 15

7.1.4 Methods for Handling Missing Data

All available efficacy and safety data will be included in data listing and tabulations. No imputation of values for missing data will be performed unless otherwise specified.

- For UFS-QoL and WPAI, published scoring manuals and guidelines will be used to calculate UFS-QoL and WPAI scale scores and handle missing data (see Appendix 3 and 4, respectively).
- For myoma or uterus volume, if D1 and D2 of the myoma or uterus are present but D3 is missing, then the volume will be calculated as D1*D2*D2*π/6 (cm^3).
- For LH, FSH, E_2, P and clinical laboratory tests, values less than the lower limit of quantification will be treated as zero when calculating the descriptive statistics.
- Disease duration with first diagnosis date of uterine fibroid that are completely or partially missing will be derived as follows:
  1. If the year is missing, then the disease duration will be treated as missing.
  2. If the year is present but the month is missing, then the month will be treated as January for the calculation.

7.2 Analysis Sets

Refer to the Handling Rules for Analysis Data.

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis

Variable(s) : Date first subject signed informed consent form
Date of last subject's last visit/contact
MedDRA version
WHO Drug version
SAS version used for creating the datasets

Analytical

Method(s) : (1) Study Information
Study information shown in the analysis variables section will be provided.

7.3.2 Screen Failures

Analysis Set: All Subjects Who Were Not Randomized

Analysis

Variable(s) :	Age (years)	[20<= - <30, 30<= - <40, 40<= - <50, 50<= - <=Max]

Analytical

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

7.3.3 Subject Eligibility

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis

Variable(s) :	Eligibility status	[Eligible for Randomization, Not Eligible for Randomization]
	Primary Reason for Subject Not Being Eligible	[Death, Adverse Event, Screen Failure, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Other]

Analytical

Method(s) : (1) Eligibility for Randomization
Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

7.3.4 Number of Subjects Randomized by Site and Treatment Group

Analysis Set: Randomized Set

Analysis Variable(s) :	Randomization status	[Randomized]
Stratum:	Site	[Site numbers will be used as categories]
Analytical Method(s) :	(1) Number of Subjects Randomized by Site and Treatment Group Frequency distribution will be provided for each stratum by treatment group and overall.	

7.3.5 Disposition of Subjects

Analysis Set:	Randomized Set	
Analysis Variable(s) :	Double-blind study drug administration status	[Randomized but Not Treated]
	Reason for not being treated	[Death, Adverse Event, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Lack of Efficacy, Bone Mineral Density Loss, Recovery Leading to Surgery, Reduction of HGB Concentration, Other]
	Double-Blind Study Drug Completion Status	[Completed Study Drug, Prematurely Discontinued Study Drug]
	Reason for Discontinuation of Study Drug	[Death, Adverse Event, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Lack of Efficacy, Bone Mineral Density Loss, Recovery Leading to Surgery, Reduction of HGB Concentration, Other]
	Completion Status of the Follow-	[Completed Follow-up Period,

	up Period	Prematurely Discontinued Follow-up Period]
	Reason for Discontinuation of the Follow-up Period	[Death, Adverse Event, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Lack of Efficacy, Bone Mineral Density Loss, Recovery Leading to Surgery, Reduction of HGB Concentration, Other]

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

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

7.3.6 Protocol Deviations

Analysis Set: Randomized Set

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

Analytical Method(s) : (1) Protocol Deviations

Frequency distribution will be provided by treatment group and overall for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several

deviations that can be classified into the same category will be counted only once.

7.3.7 Analysis Sets

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

Analytical Method(s) :
(1) Subjects Excluded from Analysis Sets
(2) Subject Data Excluded from Analysis Sets
(3) Analysis Sets

Frequency distributions will be provided by treatment group for (1) and (2), and by treatment group and overall for (3). For (1) and (2), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

7.4 Demographic and Other Baseline Characteristics

Analysis Set:	Randomized Set	
Analysis Variable(s) :	Age (years)	[20<= - <30, 30<= - <40, 40<= - <50, 50<= - <=Max]
	Height (cm)	[Min<= - <150, 150<= - <160, 160<= - <170, 170<= - <=Max]
	Weight (kg) at Baseline	[Min<= - <50, 50<= - <60, 60<= - <70, 70<= - <80,

	80<= - <=Max]
BMI (kg/m^2) at Baseline	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <=Max]
Smoking Classification	[The subject has never smoked, The subject is a current smoker, The subject is an ex-smoker]
Birth Experience	[Yes, No]
Disease Duration (years)	[Min<= - <=1, 1< - <=3, 3< - <=5, 5< - <=10, 10< - <=Max]
Type of Uterine Fibroid	
Subserosal Fibroid	[Yes, No]
Intramural Fibroid	[Yes, No]
Submucosal Fibroid	[Yes, No]
Cervical Fibroid	[Yes, No]
Stopped Any Medications for Uterine Fibroids	[Yes, No]
Type of Medication for Uterine Fibroid	
GnRH Agonist	[Yes]
Herbal Medicine	[Yes]
Other Medicines for Uterine Fibroids	[Yes]
Any Surgery for Uterine Fibroids	[Yes, No]
Volume of Myoma at Baseline (cm^3)	[Min<= - <=28, 28< - <=170, 170< - <=700, 700< - <=Max]
Volume of Uterus at Baseline (cm^3)	[Min<= - <=28, 28< - <=170, 170< - <=700, 700< - <=Max]
PBAC Score at Baseline	[120<= - <200, 200<= - <500, 500<= - <=Max]
NRS Score at Baseline	[Min<= - <4, 4<= - <7, 7<= - <=Max]
UFS-QOL Score at Baseline	
Symptom Severity	[Min<= - <=25, 25< - <=50, 50< - <=75, 75< - <=Max]
Concern	[Min<= - <=25, 25< - <=50, 50< - <=75, 75< - <=Max]
Activities	[Min<= - <=25, 25< - <=50, 50< - <=75, 75< - <=Max]

Energy/Mood	[Min<= - <=25, 25< - <=50, 50< - <=75, 75< - <=Max]
Control	[Min<= - <=25, 25< - <=50, 50< - <=75, 75< - <=Max]
Self-consciousness	[Min<= - <=25, 25< - <=50, 50< - <=75, 75< - <=Max]
Sexual Function	[Min<= - <=25, 25< - <=50, 50< - <=75, 75< - <=Max]
HRQL Total	[Min<= - <=25, 25< - <=50, 50< - <=75, 75< - <=Max]
HGB at Baseline (g/dL)	[Min<= - <10, 10<= - <12, 12<= - <=Max]
HCT at Baseline (%)	
Serum Fe at Baseline (μg/dL)	
Serum Ferritin at Baseline (ng/mL)	
Dosage of leuprorelin vial	[1.88 mg, 3.75 mg]

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

7.5 Medical History and Concurrent Medical Conditions

Analysis Set: Safety Analysis Set

Analysis Variable(s) : Medical History
Concurrent Medical Conditions

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

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

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

7.6 Medication History and Concomitant Medications

Analysis Set: Safety Analysis Set

Analysis Variable(s): Medication History
Concomitant Medications

Analytical Method(s):
(1) Medication History by Preferred Medication Name
(2) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by Preferred Medication Name

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

7.7 Study Drug Exposure and Compliance

Analysis Set: Safety Analysis Set

Analysis Variable(s):		
	Duration of Exposure to Double-Blind Study Drug (days)	[1<= - <=14, 15<= - <=42, 43<= - <=84, 85<= - <=168 169<= - <=Max]
	Double-Blind Study Drug Compliance (%)	[Min<= - <80, 80<= - <90, 90<= - <=Max]
	Maximum Drug Holidays (days)	[0, 1<= - <4, 4<= - <=Max]
	Exposure to Double-Blind leuprorelin vial (times)	[0, 1, 2, 3, 4, 5, 6]

Analytical
Method(s) : (1) Study Drug Exposure and Compliance
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by treatment group and overall.

7.8 Efficacy Analysis

7.8.1 Primary Efficacy Endpoint(s)

7.8.1.1 Primary Analysis

Analysis Set: Full Analysis Set
Analysis
Variable(s): Proportion of subjects with a total PBAC score of < 10 from Week 6 to 12
Analytical Method(s): The point estimate and 2-sided 95% confidence interval of 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), using Farrington and Manning (FM) method. In addition, non-inferiority test using FM method with a non-inferiority margin of 15% will be conducted for the comparison between TAK-385 40 mg group and leuprorelin group. If the lower bound of the 95%CI is greater or equal to the non-inferiority margin of -15%, then non-inferiority of TAK-385 40mg to leuprorelin will be concluded.

7.8.1.2 Secondary Analysis

Analysis Set: Per Protocol Set
Analysis
Variable(s): Proportion of subjects with a total PBAC score of < 10 from Week 6 to 12
Analytical
Method(s): An analysis similar to the above “Primary analysis” will be performed

using the PPS to assess the robustness of the results.

7.8.1.3 Adjustments for Covariates

Analysis Set:	Full Analysis Set	
Analysis Variable(s):	Proportion of subjects with a total PBAC score of < 10 from Week 6 to 12	
Covariate(s):	PBAC Score at Baseline	[120<= - <200, 200<= - <500, 500<= - <=Max]
Analytical Method(s):	The difference between groups in the proportion of subjects with a total PBAC score of < 10 from Week 6 to 12 will be analyzed using binomial regression with the identity link that includes treatment group and PBAC score at baseline as independent categorical variable.	

7.8.1.4 Examination of Subgroups

Analysis Set:	Full Analysis Set	
Analysis Variable(s):	Proportion of subjects with a total PBAC score of < 10 from Week 6 to 12	
Subgroup(s):	Age (years)	[20<= - <30, 30<= - <40, 40<= - <50, 50<= - <=Max]
	BMI (kg/m^2) at Baseline	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <=Max]
	PBAC Score at Baseline	[120<= - <200, 200<= - <500, 500<= - <=Max]
	Birth Experience	[Yes, No]
	Volume of Uterus at Baseline (cm^3)	[Min<= - <=28, 28< - <=170, 170< - <=700, 700< - <=Max]
	Type of Uterine Fibroid	
	Subserosal Fibroid	[Yes, No]
	Intramural Fibroid	[Yes, No]
	Submucosal Fibroid	[Yes, No]

Analytical
Method(s): (1) Descriptive Statistics
The point estimate and 2-sided 95% confidence interval of the proportion of subjects with a total PBAC score of < 10 from Week 6 to 12 will be summarized for above each subgroup by treatment group.

7.8.2 Secondary Efficacy Endpoint(s)

7.8.2.1 PBAC Score

Analysis Set: Full Analysis Set
Analysis
Variable(s): Proportion of subjects with a total PBAC score of < 10 from Week 2 to 6
Proportion of subjects with a total PBAC score of < 10 from Week 18 to 24
Proportion of subjects with a total PBAC score of < 10 for 6 weeks before the final dose of study drug
Analytical
Method(s): For each variable, 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, using FM method with the non-inferiority margin of -15%. The confidence interval will be presented in a descriptive manner and not for the purpose of statistical inference.

7.8.2.2 Myoma Volumes and Uterine Volumes

Analysis Set: Full Analysis Set
Analysis
Variable(s): Myoma volumes
Uterine volumes
Visit: Baseline, Week 2, 4, 8, 12 and 24
Analytical
Method(s): For each variable, descriptive statistics will be provided for the observed values and the percent changes from baseline by treatment group for

each visit.
The mean differences in the percent changes from baseline between TAK-385 40 mg and leuprorelin group and the two-sided 95% confidence intervals will be provided.

7.8.2.3 Hemoglobin

Analysis Set:	Full Analysis Set	
Analysis Variable(s):	HGB (g/dL)	[Min<= - <12, 12<= - <=Max]
	Change from baseline on HGB (g/dL)	[Min<= - <1, 1<= - <=Max]
Subgroup(s):	Oral iron preparation use at baseline	[Yes, No]
	HGB at Baseline (g/dL)	[Min<= - <12, 12<= - <=Max]
Visit:	Baseline, Week 4, 8, 12, 16, 20, 24 and Follow-up	

Analytical Method(s): Summary statistics will be provided for the observed values and the changes from baseline by treatment group for each visit.
The mean differences in the change from baseline between TAK-385 40 mg and leuprorelin groups and the two-sided 95% confidence intervals will be provided for each visit.
For categorical variables, frequency will be summarized by treatment group for each visit. The differences in the percentage between TAK-385 40 mg and leuprorelin groups and the two-sided 95% confidence intervals will be provided for each visit.
Additionally, the above mentioned analysis will also be conducted for each subgroup.

7.8.2.4 NRS Score

Analysis Set: Full Analysis Set
Analysis Variable(s): NRS score from Week 6 to 12

NRS score from Week 2 to 6
NRS score from Week 18 to 24
NRS score for 6 weeks before the final dose

Analytical Method(s): For each variable, summary statistics will be provided by treatment group. Two-sided 95% confidence interval of the difference will be calculated between TAK-385 40 mg and leuprorelin group.

7.8.2.5 UFS-QOL Score

Analysis Set: Full Analysis Set

Analysis Variable(s): Symptom Severity
Concern
Activities
Energy/Mood
Control
Self-consciousness
Sexual Function
HRQL Total

Visit: Baseline , Week 4, 8, 12, 16, 20, 24 and Follow-up

Analytical Method(s): For each variable, descriptive statistics will be provided for the observed values and the changes from baseline by treatment group for each visit. The mean differences in the observed values between TAK-385 40 mg and leuprorelin group and the two-sided 95% confidence intervals will be provided for each visit.

7.8.3 Additional Efficacy Endpoint(s)

7.8.3.1 Hematocrit, Serum Fe, and Serum Ferritin

Analysis Set: Full Analysis Set

Analysis Variable(s): HCT

	Serum Fe
	Serum ferritin
Visit:	Baseline , Week 4, 8, 12, 16, 20, 24 and Follow-up
Analytical Method(s):	For each variable, summary statistics will be provided for the observed values and the changes from baseline by treatment group for each visit.

7.8.3.2 Use of Analgesic Medications During the Treatment

Analysis Set:	Full Analysis Set
Analysis Variable(s):	Use of analgesic medications during the Treatment from Week 6 to 12 Use of analgesic medications during the Treatment from Week 2 to 6 Use of analgesic medications during the Treatment from Week 18 to 24 Use of analgesic medications during the Treatment for 6 weeks before the final dose
Analytical Method(s):	For each variable, summary statistics will be provided by treatment group.

7.8.3.3 WPAI:GH During the Treatment

Analysis Set:	Full Analysis Set
Analysis Variable(s):	Absenteeism Presenteeism Work productivity loss Activity impairment
Visit:	Baseline , Week 2, 4, 8, 12 and 24
Analytical Method(s):	For each variable, summary statistics will be provided for the observed values and the changes from baseline by treatment group for each visit. The mean differences in the observed values between TAK-385 40 mg and leuprorelin group and the two-sided 95% confidence intervals will be provided for each visit.

7.8.3.4 Amenorrhea (The subject with a total PBAC score of 0)

Analysis Set: Full Analysis Set

Analysis Variable(s): Proportion of subjects with a total PBAC score of 0 from Week 6 to 12
Proportion of subjects with a total PBAC score of 0 from Week 2 to 6
Proportion of subjects with a total PBAC score of 0 from Week 18 to 24
Proportion of subjects with a total PBAC score of 0 for 6 weeks before the final dose of study drug

Analytical Method(s): For each variable, 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, using FM method with the non-inferiority margin of -15%. The confidence interval will be presented in a descriptive manner and not for the purpose of statistical inference.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

Not applicable

7.9.2 Pharmacodynamic Analysis

7.9.2.1 LH, FSH, E_2, and P

Analysis Set: Full Analysis Set

Analysis Variable(s) : LH
FSH
E_2
P

Visit: Baseline , Week 2, 4, 8, 12, 16, 20, 24 and Follow-up

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

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

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

7.10 Other Outcomes

Not applicable

7.11 Safety Analysis

7.11.1 Adverse Events

7.11.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	Treatment-emergent adverse event (TEAE)	
Categories:	Relationship to Study Drug	[Related, Not Related]
	Intensity	[Mild, Moderate, Severe]

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

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

study drug (number of events, number and percentage of subjects)

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

TEAEs will be counted according to the rules below.

Number of subjects

- Summaries for 2) and 6)
  A subject with occurrences of TEAE in both categories (ie, Related and Not Related) will be counted once in the Related category.
- Summary for 3)
  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.
- Summaries other than 2) , 3) , and 6)
  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

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

7.11.1.2 Displays of Treatment-Emergent Adverse Events

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	TEAE	
Categories:	Intensity	[Mild, Moderate, Severe]
	Time of Onset (day)	[1<= - <=28, 29<= - <=56, 57<= - <=84, 85<= - <=112, 113<= - <=140, 141<= - <=168, 169<= - <=Max]
Analytical Method(s) :	The following summaries will be provided using frequency distribution	

for each treatment group.

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

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

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(2) Treatment-Emergent Adverse Events by System Organ Class
(3) Treatment-Emergent Adverse Events by Preferred Term
(4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(6) Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term
(7) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term
(8) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(9) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Over Time
(10) Most Frequent Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(11) Most Frequent Non-Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

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

<u>Number of subjects</u>

- Summary tables other than (5), (6) and (9)
  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT.

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

- Summary tables for (5) and (6)
  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages will be based on the number of subjects in the safety analysis set.
- Summary table for (9)
  A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT.
  When calculating percentages for each time interval, the number of subjects at risk (ie, subjects who either have an exposure or have an occurrence of TEAE, during or after the corresponding time interval) will be used as the denominator. The number of subjects whose onset of any one of the TEAEs is within the time interval will be used as the numerator.
- Summary table for (10)
  Most frequent TEAEs refer to PTs whose percentages are at least 5.0% in any one of the treatment groups.
- Summary table for (11)
  Most frequent Non-Serious TEAEs refer to PTs whose percentages are at least 5.0% in any one of the treatment groups. If no Non-Serious TEAEs exceed a frequency of 5.0%, the frequency cutoff of 2.0% will be used instead. Percentages will be based on the number of subjects in the safety analysis set.

7.11.1.3 Displays of Pretreatment Events

Analysis Set: All Subjects Who Signed the Informed Consent Form
Analysis
Variable(s) : Pretreatment event (PTE)
Analytical The following summaries will be provided using frequency distribution.

Method(s) : PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

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

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

Number of subjects

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

7.11.1.4 Displays of Run-in Adverse Events

Analysis Set: All Subjects Who Received Run-in Study Drug

Analysis

Variable(s) : Run-in AE

Analytical Method(s) : The following summaries will be provided using frequency distribution. Run-in AEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) Run-in Adverse Events by System Organ Class and Preferred Term
(2) Drug-Related Run-in Adverse Events by System Organ Class and Preferred Term
(3) Serious Run-in Adverse Events by System Organ Class and Preferred Term

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

Number of subjects

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

7.11.2 Clinical Laboratory Evaluations

7.11.2.1 Hematology and Serum Chemistry

Analysis Set: Safety Analysis Set

Analysis Variable(s) :

Hematology

RBC	Platelets	WBC
WBC Differentials (Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes)		

Serum Chemistry

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
Bile acid (total bile acid [TBA])	Glutamate dehydrogenase (GLDH)	

Visit: Baseline, Week 2*, 4, 8, 12, 16, 20, 24 and Follow-up
*: only TBA and GLDH

Analytical Method(s) : For each variable, summaries (1) to (3) will be provided by treatment group.
For applicable variables, summaries (4) and (5) will be provided by treatment group.

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

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

(3) Summary of Shifts of Laboratory Test Results
Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.
For each laboratory test, the laboratory values will be classified as "Low", "Normal" or "High" relative to the normal reference range provided by the central laboratory. The shift tables will be based on these classifications.

(4) Number and Percentage of Subjects with Markedly Abnormal Values of Laboratory Parameters
Overall frequency distributions of MAV during treatment period will be provided. If a laboratory parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

(5) Number and Percentage of Subjects with Elevated Liver Enzyme Laboratory Parameters
Overall frequency distributions of elevated hepatic parameters during treatment period will be provided. Further details are given in Appendix.

7.11.2.2 Urinalysis

Analysis Set: Safety Analysis Set

Analysis Variable(s) :

Protein	[-, +-, 1+, 2+, 3+, 4+]
Glucose	[-, 1+, 2+, 3+, 4+, 5+]
Occult blood	[-, +-, 1+, 2+, 3+]
Bilirubin	[-, +-, 1+, 2+, 3+]
Urobilinogen	[+-, 1+, 2+, 3+]

Visit: Baseline , Week 4, 8, 12, 16, 20, 24 and Follow-up

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

(1) Number of Subjects in Categories of Urine Laboratory Test Results
Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

(2) Summary of Shifts of Urine Laboratory Test Results
Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.
For each urine laboratory test, the laboratory values will be classified as "Normal" or " Abnormal " relative to the normal reference range provided by the central laboratory. The shift tables will be based on these classifications.

7.11.3 Vital Signs

7.11.3.1 Vital Signs and Weight

Analysis Set: Safety Analysis Set

Analysis Variable(s) : Systolic Blood Pressure
Diastolic Blood Pressure
Pulse Rate
Body temperature
Weight

Visit: Baseline , Week 4, 8, 12, 16, 20, 24 and Follow-up

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

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

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

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

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

7.11.4 12-Lead ECGs

7.11.4.1 12-lead ECG

Analysis Set: Safety Analysis Set
Analysis
Variable(s) : 12-lead ECG Interpretation [Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]
Visit: Baseline , Week24 and Follow-up
Analytical
Method(s) : For 12-lead ECG interpretation, summary (1) will be provided by treatment group.

(1) Summary of Shift of 12-lead ECG Interpretation
Shift table showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

7.11.5 Other Observations Related to Safety

7.11.5.1 Bone Mineral Density and Biochemical Bone Metabolism Markers

Analysis Set: Safety Analysis Set
Analysis
Variable(s) : T score [Min <= -<=-2.500,

		-2.499<= - <=-1.000, -0.999<= - <= MAX]
	Bone Mineral Density (g/cm^2)	
	Percent Change from baseline on Bone Mineral Density (%)	[Min<= - <-7, -7<= - <=Max]
	NTELOP (nmol BCE/L)	
	Bone Type Alkaline Phosphatase (μg/L)	
Visit:	Baseline , Week 12, 24	
Analytical Method(s) :	For each variable except T score, summaries (1), (3), and (4) will be provided by treatment group. For T score, summary (2), (3), (4), and (5) will be provided by treatment group. (1) Summary of Parameters and percent Change from Baseline by Visit Descriptive statistics for observed values for each visit and percent changes from baseline will be provided. For categorical variables, frequency will be summarized by treatment group for each visit. (2) Summary of Parameters and Change from Baseline by Visit Descriptive statistics for observed values for each visit and changes from baseline will be provided. (3) Case Plots Plots over time for each subject will be presented. (4) Mean Plot with Standard Deviations For T score, mean of observed values and changes from baseline will be plotted by visit. For other variables, mean of observed values and percent changes from baseline will be plotted by visit. (5) Summary of Shift of T score Shift table showing the number of subjects in each category at baseline and each post-baseline visit will be provided.	

7.11.5.2 Return of Menstrual Cycles

Analysis Set: Safety Analysis Set

Analysis

Variable(s) : Duration of Menstruation Recovery (Days)

Analytical

Method(s) : Summary (1) will be provided by treatment group.

(1) Summary of Duration of Menstruation Recovery

Descriptive statistics for observed values will be provided.

7.12 Interim Analysis

Not applicable

7.13 Changes in the Statistical Analysis Plan

Change from previous version are described in following table.

Page	Previous version	Current version	Reason
14	7.1.1 Study Definitions	7.1.1 Study Definitions Oral iron preparation The drug with the following drug code of WHODD: 00023503001, 00023505001, 00023520001, 00023550009, 00023550074, 90059601001	Specify the definition of Oral iron preparation based on blind review
17	7.1.4 Methods for Handling Missing Data	7.1.4 Methods for Handling Missing Data ·For LH, FSH, E2, P and clinical laboratory tests, values less than the lower limit of quantification will be treated as zero when calculating the descriptive statistics.	Specify how to deal with value with lower limit of quantification for LH, FSH, E2, P and clinical laboratory

23	7.4Demographic and Other Baseline Characteristics Other Medicines for UterineFibroids	7.4Demographic and Other Baseline Characteristics Other Medicines for Uterine Fibroids	Typo
26	7.8.1.1Primary Analysis If the lower bound of the 95%CI is greater or equal to the non-inferiority margin of 15%,, then non-inferiority of TAK-385 40mg to leuprorelin will be concluded.	7.8.1.1Primary Analysis If the lower bound of the 95%CI is greater or equal to the non-inferiority margin of -15%, then non-inferiority of TAK-385 40mg to leuprorelin will be concluded.	Typo
27	7.8.1.4Examination of Subgroups Cervical Fibroid[Yes, No]	7.8.1.4Examination of Subgroups removed	Removed based on blind review
28	7.8.2.1PBAC Score For each variable, 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, using FM method.	7.8.2.1PBAC Score For each variable, 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, using FM method with the non-inferiority margin of -15%. The confidence interval will be presented in a descriptive manner and not for the purpose of statistical inference.	Specify the detail description how to calculate CI using FM method, based on the comment.
29	7.8.2.3Hemoglobin	7.8.2.3Hemoglobin HGB at Baseline (g/dL)[Min<= - <12, 12<= - <=Max]	Added based on blind review
32		Section 7.8.3.4 was newly added.	Added based on the comment.

42	7.11.5.1Bone Mineral Density and Biochemical Bone Metabolism Markers For each variable, summaries (1) and (2) will be provided by treatment group.	7.11.5.1Bone Mineral Density and Biochemical Bone Metabolism Markers For each variable except T score, summaries (1), (3), and (4) will be provided by treatment group.	Modified based on blind review
42	7.11.5.1Bone Mineral Density and Biochemical Bone Metabolism Markers For T score, summary (3) will be provided by treatment group.	7.11.5.1Bone Mineral Density and Biochemical Bone Metabolism Markers For T score, summary (2), (3), (4), and (5) will be provided by treatment group.	Modified based on blind review
42	7.11.5.1Bone Mineral Density and Biochemical Bone Metabolism Markers Descriptive statistics for observed values for each visit and changes from baseline will be provided.	7.11.5.1Bone Mineral Density and Biochemical Bone Metabolism Markers Descriptive statistics for observed values for each visit and percent changes from baseline will be provided.	Modified based on blind review
42	7.11.5.1Bone Mineral Density and Biochemical Bone Metabolism Markers	7.11.5.1Bone Mineral Density and Biochemical Bone Metabolism Markers (2)Summary of Parameters and Change from Baseline by Visit Descriptive statistics for observed values for each visit and changes from baseline will be provided.	Modified based on blind review
43	7.11.5.1Bone Mineral Density and Biochemical Bone Metabolism Markers	7.11.5.1Bone Mineral Density and Biochemical Bone Metabolism Markers (4)Mean Plot with Standard Deviations	Modified based on blind review

		For T score, mean of observed values and changes from baseline will be plotted by visit. For other variables, mean of observed values and percent changes from baseline will be plotted by visit.	
45	Appendix 1. Criteria for Markedly Abnormal Values For each parameter, all evaluable data (i.e., non-missing and acceptable according to the Handling Rules for Analysis Data) obtained up to Follow-up Day 14 will be classified as a MAV or not.	Appendix 1. Criteria for Markedly Abnormal Values For each parameter, all evaluable data (i.e., non-missing and acceptable according to the Handling Rules for Analysis Data) obtained up to Follow-up Day 42 will be classified as a MAV or not.	Modified to be accordance with CCT-001 study.
46	Appendix 1. Criteria for Markedly Abnormal Values Pulse (bpm)	Appendix 1. Criteria for Markedly Abnormal Values Pulse Rate (bpm)	Typo
46	Appendix 1. Criteria for Markedly Abnormal Values Body Temperature (°C)	Appendix 1. Criteria for Markedly Abnormal Values Body temperature (°C)	Typo
48	Appendix 2. Criteria for Elevated Liver Enzyme All evaluable data (ie, non-missing and acceptable according to the Handling Rules for Analysis Data) obtained up to Follow-up Day 14 will be used to determine whether each criteria for elevated liver enzyme in the table below is met or not.	Appendix 2. Criteria for Elevated Liver Enzyme All evaluable data (ie, non-missing and acceptable according to the Handling Rules for Analysis Data) obtained up to Follow-up Day 42 will be used to determine whether each criteria for elevated liver enzyme in the table below is met or not.	Modified to be accordance with CCT-001 study.
52	Appendix 3. UFS-QoL Scoring Manual	Appendix 3. UFS-QoL Scoring Manual	Modified based on blind review

	Transformed Score =((Actual raw score – lowest possible raw score)/(Possible raw score range))*100	Transformed Score =((Actual raw score – lowest possible raw score)/(Possible raw score range))*100 (rounded to the nearest integer)	
53	Appendix 3. UFS-QoL Scoring Manual Transformed Score =((Highest possible score – Actual raw score)/(Possible raw score range))*100	Appendix 3. UFS-QoL Scoring Manual Transformed Score =((Highest possible score – Actual raw score)/(Possible raw score range))*100 (rounded to the nearest integer)	Modified based on blind review
54	Appendix 4. WPAI Scoring Manual Multiply scores by 100 to express in percentages.	Appendix 4. WPAI Scoring Manual Multiply scores by 100 to express in percentages (rounded to the nearest integer).	Modified based on blind review

8.0 REFERENCES

Farrington C P, Manning G: Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Statistics in Medicine 1990; 9: 1447-1454.