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-385-3008

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

PHASE 3

Version**:** Amended

Date**:** 1 SEP 2017

Prepared by:

[redacted]

[redacted]

Based on:

Protocol Version: Original

Protocol Date: 3 December 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
BMD	bone mineral density
BMI	body mass index
BUN	blood urea nitrogen
Cmax	maximum observed plasma concentration
CRF	case report form
CRO	contract research organization
CT	computed tomography
E2	estradiol
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDA	Food and Drug Administration
Fe	iron
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GnRH	gonadotropin-releasing hormone
HGB	hemoglobin
HDL	high density lipoprotein
hCG	human chorionic gonadotropin
HCT	hematocrit
ICH	International Conference on Harmonisation
INN	international non-proprietary name
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LFT	liver function test
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
NILM	negative for intraepithelial lesion or malignancy

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

4.0 OBJECTIVES

4.1 Primary Objective

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

4.2 Secondary Objective

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

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

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

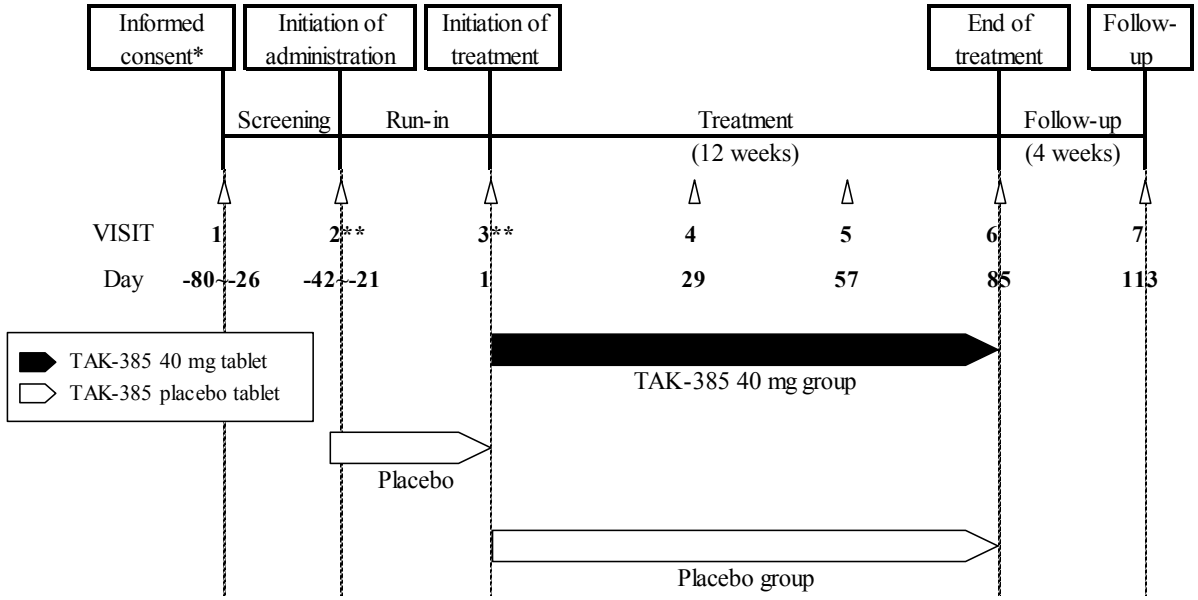
After signing the informed consent form, subjects will start recording in the patient diary from the day of VISIT 1. During the period between VISIT 2 and VISIT 3, in which subjects must experience 1 menstrual cycle, the baseline values for the efficacy evaluation of pain symptoms (baseline NRS score: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

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

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 placebo group. Study drug (TAK-385 40 mg or TAK-385 placebo) will be administered from the day of VISIT 3 to the day before VISIT 6 (or until early termination) under double-blind conditions.

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

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

5.2 Secondary Endpoints

1) Efficacy:

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

2) Safety:

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

5.3 Additional Endpoints

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

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

6.0 DETERMINATION OF SAMPLE SIZE

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

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

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

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 2-sided and will be assessed at α=0.05 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 double-blind study drugs taken/duration of exposure to double-blind study 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 study drug for the treatment period

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

((number of subjects with a maximum NRS score of 1 or less during the last 28 days of the treatment)/(number of subjects with available data during the 27 days before the final dose of study drug and the date))*100 (rounded to 1 decimal places)
Similarly, for proportion of subjects with a maximum NRS score of 0 during the 27 days before the final dose of study drug and the date, its numerator will be defined as number of subjects with a maximum NRS score of 0 during the 27 days before the final dose of study drug and the date.

Number of days without pain symptoms (NRS = 0) during the 28 days before the final dose of study drug (%):

((number of days without pain symptoms (NRS = 0) during the last 28 days of the treatment)/(number of days with available data during the last 28 days of the treatment))*100 (rounded to 1 decimal places)

Maximum NRS score at baseline

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

Mean NRS score at baseline

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

Maximum NRS score from Day 1 to 28, 29 to 56, and 57 to 84

Maximum NRS score from Day 1 to earlier of Day 28 or Follow-up Day 3.
Similarly, Maximum NRS score from Day 29 to 56 and from Day 57 to 84 will be defined as maximum NRS score from Day 29 to earlier of Day 56 or Follow-up Day 3 and from Day 57 to earlier of Day 84 or Follow-up Day 3, respectively.

Mean NRS score from Day 1 to 28, 29 to 56, and 57 to 84

Mean NRS score from Day 1 to earlier of Day 28 or Follow-up Day 3.
Similarly, Mean NRS score from Day 29 to 56 and from Day 57 to 84 will be defined as mean NRS score from Day 29 to earlier of Day 56 or Follow-up Day 3 and from Day 57 to earlier of Day 84 or Follow-up Day 3, respectively.

Number of days without pain symptoms (NRS = 0) from Day 1 to 28, 29 to 56, and 57 to 84

((number of days without pain symptoms (NRS = 0) from Day 1 to earlier of Day 28 or Follow-up Day 3)/(number of days with available data from Day 1 to earlier of Day 28 or Follow-up Day 3))*100 (rounded to 1 decimal places)
Number of days without pain symptoms (NRS = 0) from Day 29 to 56 and from Day 57 to 84 will be derived in a similar manner.

Use of analgesic medications during the 28 days before the final dose of study drug

((number of days with analgesic medications use during the last 28 days of the treatment)/(number of days with available data during the last 28 days of the treatment))*100 (rounded to 1 decimal places)

Myoma volumes

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

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

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 UFS-QOL score

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-80 - 1	
Week 12	Study Day: 85	2 - 99	< 4

Pharmacodynamic measurements

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	< 4

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Week 8	Study Day: 57	44 – 71	< 4
Week 12	Study Day: 85	72 – 99	< 4
Follow-up	Follow-up Day: 28	2 <=	4 – 42

Clinical laboratory tests 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
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 12	Study Day: 85	2 – 99	< 15
Follow-up	Follow-up Day: 28	2 <=	15 – 42

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, published scoring manuals and guidelines will be used to calculate UFS-QoL and handle missing data (see Appendix 3).
- 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 $D1*D2*D2*\pi/6$ (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	Double-Blind Study Drug	
Variable(s) :	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, 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, Other]
Completion Status of the Follow-up Period	[Completed Follow-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, 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	

UterineFibroids	[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]
Maximum NRS Score at Baseline	[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]

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<= - <= Max]

Double-Blind Study Drug Compliance (%)	[Min<= - <80, 80<= - <90, 90<= - <=Max]
Maximum Drug Holidays (days)	[0, 1<= - <4, 4<= - <=Max]

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

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

Analytical Method(s): The proportion of subjects with a maximum NRS score of 1 or less during the 28 days before the final dose of study drug will be summarized by treatment group. The primary analysis will be based on the comparison between the treatment groups using a Fisher's exact test. The point estimate and 2-sided 95% confidence interval of odds ratio will be calculated between TAK-385 40 mg group and placebo group (TAK-385 40 mg group / placebo group).

7.8.1.2 Secondary Analysis

Analysis Set: Per Protocol Set

Analysis Variable(s): Proportion of subjects with a maximum NRS score of 1 or less during the 28 days before the final dose of study drug

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 Examination of Subgroups

Analysis Set: Full Analysis Set

Analysis Variable(s): Proportion of subjects with a maximum NRS score of 1 or less during the 28 days before the final dose of study drug

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]
	Birth Experience	[Yes, No]
	Volume of Uterus at Baseline (cm^3)	[Min<= - <=28, 28< - <=170, 170< - <=700, 700< - <=Max]
	Maximum NRS Score at Baseline	[4<= - <7, 7<= - <=Max]
	Type of Uterine Fibroid	
	Subserosal Fibroid	[Yes, No]
	Intramural Fibroid	[Yes, No]

Analytical Method(s): (1) Descriptive Statistics

The point estimate and 2-sided 95% exact confidence interval of the proportion of subjects with a maximum NRS score of 1 or less during the 28 days before the final dose of study drug will be summarized for above each subgroup by treatment group.

7.8.2 Secondary Efficacy Endpoint(s)

7.8.2.1 NRS Score

Analysis Set: Full Analysis Set

Analysis Variable(s): Proportion of subjects with a maximum NRS score of 0 during the 28 days before the final dose of study drug

Mean NRS score during the 28 days before the final dose of study drug
Number of days without pain symptoms (NRS = 0) during the 28 days before the final dose of study drug

Analytical Method(s):

(1) Proportion of subjects with a maximum NRS score of 0 during the 28 days before the final dose of study drug will be summarized by treatment group. The point estimate and 2-sided 95% confidence interval of odds ratio will be calculated between TAK-385 40 mg group and placebo group (TAK-385 40 mg group / placebo group).

(2) For mean NRS score and number of days without pain symptoms (NRS = 0), descriptive statistics will be provided for the observed values and the change from baseline by treatment group. The mean differences between TAK-385 40 mg group and placebo group and the two-sided 95% confidence intervals will be provided.

7.8.2.2 NRS Score time course

Analysis Set: Full Analysis Set

Analysis Variable(s): Proportion of subjects with a maximum NRS score of 1 or less
Proportion of subjects with a maximum NRS score of 0
Mean NRS score
Number of days without pain symptoms (NRS = 0)

Visit: Baseline, Day 1 to 28, Day 29 to 56, Day 57 to 84

Analytical Method(s): Summaries (1) and (2) will be provided by each visit.

(1) Proportion of subjects with a maximum NRS score of 1 or less and proportion of subjects with a maximum NRS score of 0 will be summarized by treatment group. The point estimate and 2-sided 95% confidence interval of odds ratio will be calculated between TAK-385 40 mg group and placebo group (TAK-385 40 mg group / placebo group).

(2) For mean NRS score and number of days without pain symptoms (NRS = 0), descriptive statistics will be provided for the observed values and the change from baseline by treatment group. The mean differences between TAK-385 40 mg group and placebo group and the two-sided 95% confidence intervals will be provided.

7.8.3 Additional Efficacy Endpoint(s)

7.8.3.1 Myoma Volumes and Uterine Volumes

Analysis Set:	Full Analysis Set
Analysis Variable(s):	Myoma volumes Uterine volumes
Visit:	Baseline , Week 12
Analytical Method(s):	For each variable, descriptive statistics will be provided for the observed values and the percent changes from baseline by treatment group. The mean differences in the percent changes from baseline between TAK-385 40 mg group and placebo group and the two-sided 95% confidence intervals will be provided.

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 28 days before the final dose of study drug
Analytical Method(s):	Descriptive statistics will be provided by treatment group.

7.8.3.3 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 12

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

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 4, 8, 12 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): 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 (i.e., Related and Not Related) will be counted once in the Related category.
- Summary for 3)
  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.
- Summaries other than 2) , 3) , and 6)
  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

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

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<= - <=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 (i.e., subjects who either have an exposure or have an occurrence of TEAE, during or after the corresponding time interval) will be used as the denominator. The number of subjects whose onset of any one of the TEAEs is within the time interval will be used as the numerator.

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

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

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 WBC

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

HGB Hematocrit (HCT) Platelets

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

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

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 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 and Follow-up

Analytical Method(s): For each variable, summaries (1) and (2) will be provided by treatment group.
For applicable variables, summaries (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 , Week12 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 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

Page	Previous version	Current version	Reason
12	7.1.1 Study Definitions Number of days without pain symptoms (NRS = 0) during the 28 days before the final dose of study drug	7.1.1 Study Definitions Number of days without pain symptoms (NRS = 0) during the 28 days before the final dose of study drug (%):	Typo
12	7.1.1 Study Definitions	7.1.1 Study Definitions Added the definition of Maximum NRS score at baseline, Mean NRS score at baseline, Maximum NRS score from Day 1 to 28 and Mean NRS score from Day 1 to 28 Number of days without pain symptoms (NRS = 0) from Day 1 to 28	Based on the comment from team member, added.
15	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.	Based on the comment from team member, added.
17	7.3.5Disposition of Subjects [Randomize but Not Treated]	7.3.5Disposition of Subjects [Randomized but Not Treated]	Typo
19	7.4Demographic and Other Baseline Characteristics Weight at Baseline (kg)	7.4Demographic and Other Baseline Characteristics Weight (kg) at Baseline	Typo
19	7.4Demographic and Other Baseline Characteristics BMI at Baseline (kg/m2)	7.4Demographic and Other Baseline Characteristics BMI (kg/m2) at Baseline (kg/m2)	Typo

Page	Previous version	Current version	Reason
22	7.7Study Drug Exposure and Compliance Duration of exposure to double-blind study drug (days)	7.7Study Drug Exposure and Compliance Duration of Exposure to Double-Blind Study Drug (days)	Typo
22	7.7Study Drug Exposure and Compliance Double-blind study drug compliance (%)	7.7Study Drug Exposure and Compliance Double-Blind Study Drug Compliance (%)	Typo
22	7.7Study Drug Exposure and Compliance Maximum drug holidays (days)	7.7Study Drug Exposure and Compliance Maximum Drug Holidays (days)	Typo
23	7.8.1.3Examination of Subgroups BMI at Baseline (kg/m2)	7.8.1.3Examination of Subgroups BMI (kg/m2) at Baseline	Typo
23	7.8.1.3Examination of Subgroups Maximum NRS score at baseline	7.8.1.3Examination of Subgroups Maximum NRS Score at Baseline	Typo
23	7.8.1.3Examination of Subgroups Submucosal Fibroid[Yes, No] Cervical Fibroid[Yes, No]	7.8.1.3Examination of Subgroups （削除）	Modified based on the blind review
24	7.8.2.1NRS Score (1)Proportions of subjects with a maximum NRS score of 0 during ...	7.8.2.1NRS Score (1)Proportion of subjects with a maximum NRS score of 0 during ...	Typo
24	7.8.2.1NRS Score (2)For mean NRS score and number of days without pain symptoms (NSR = 0),	7.8.2.1NRS Score (2)For mean NRS score and number of days without pain symptoms (NRS = 0),	Typo

Page	Previous version	Current version	Reason
24	7.8.2.2NRS Score time course Proportion of subjects with a maximum NRS score of 0	7.8.2.2NRS Score time course Proportion of subjects with a maximum NRS score of 1 or less	Typo
25	7.8.2.2NRS Score time course Proportion of subjects with a maximum NRS score of 1	7.8.2.2NRS Score time course Number of days without pain symptoms (NRS = 0)	Typo
25	7.8.2.2NRS Score time course Day 1 to 28, Day 29 to 56, Day 57 to 84	7.8.2.2NRS Score time course Baseline, Day 1 to 28, Day 29 to 56, Day 57 to 84	Based on the comment from team member, added.
25	7.8.2.2NRS Score time course (1)Proportions of subjects with a maximum NRS score of 0 will be summarized by treatment group. The point estimate and 2-sided 95% confidence interval of odds ratio will be calculated between TAK-385 40 mg group and placebo group (TAK-385 40 mg group / placebo group).	7.8.2.2NRS Score time course (1)Proportion of subjects with a maximum NRS score of 1 or less and proportion of subjects with a maximum NRS score of 0 will be summarized by treatment group. The point estimate and 2-sided 95% confidence interval of odds ratio will be calculated between TAK-385 40 mg group and placebo group (TAK-385 40 mg group / placebo group).	Typo
25	7.8.2.2NRS Score time course (2)For mean NRS score and number of days without pain symptoms (NSR = 0),	7.8.2.2NRS Score time course (2)For mean NRS score and number of days without pain symptoms (NRS = 0),	Typo
38	Appendix 1. Criteria for Markedly Abnormal Values up to Follow-up Day 14 will be classified as a MAV or	Appendix 1. Criteria for Markedly Abnormal Values up to Follow-up Day 42 will be classified as a MAV or	Modified based on the comment from team member.

Page	Previous version	Current version	Reason
	not.	not.	
41	Appendix 2. Criteria for Elevated Liver Enzyme obtained up to Follow-up Day 14 will be used to determine whether each criteria	Appendix 2. Criteria for Elevated Liver Enzyme obtained up to Follow-up Day 42 will be used to determine whether each criteria	Modified based on the comment from team member.

8.0 REFERENCES