This is the translated version of the Clinical Study Protocol written in Japanese.

Clinical Study Protocol

Study Title:	A Phase III Confirmatory Study of KLH-2109 in Uterine Fibroid Patients with Menorrhagia and Pain
Protocol Number:	KLH2302
Version:	2.0
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Sponsor:	Kissei Pharmaceutical Co., Ltd. Koishikawa 3-1-3, Bunkyo-ku, Tokyo [redacted]
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Protocol Synopsis

Study Title:
A Phase III Confirmatory Study of KLH-2109 in Uterine Fibroid Patients with Menorrhagia and Pain
(Protocol Number: KLH2302)

Study Phase:
III

Study Objectives:
1. Primary objective
To confirm the superiority of KLH-2109 200 mg orally once daily for 12 weeks to placebo for efficacy against menorrhagia and pain symptoms in uterine fibroid patients with menorrhagia and pain symptoms in a double-blind manner
2. Secondary objectives
• To evaluate the improvement in menorrhagia
• To evaluate the improvement in pain symptoms associated with uterine fibroids
• To evaluate the improvement in anaemia
• To evaluate reduction of myoma volume and uterine volume
• To evaluate the improvement in quality of life (QOL) associated with uterine fibroids
• To evaluate safety
• To evaluate pharmacokinetics
• To evaluate pharmacodynamic effect

Endpoints:
1. Primary endpoint
• Proportion of subjects with a total Pictorial Bleeding Assessment Chart (PBAC) score of <10 from Week 6 to Week 12 after administration of the investigational product
• Proportion of subjects with the maximum numerical rating scale (NRS) score for pain symptoms of ≤1 for 28 days prior to the end of the investigational product administration
2. Secondary endpoints
• Proportion of subjects with a total PBAC score of <10 from Week 2 to Week 6 after administration of the investigational product
• Proportion of subjects with a total PBAC score of <10 for 6 weeks prior to the end of the investigational product administration
• Time to a total PBAC score of <10
• Proportion of subjects with amenorrhoea (a total PBAC score of 0) from Week 2 to Week 6 after administration of the investigational product
• Proportion of subjects with amenorrhoea (a total PBAC score of 0) from Week 6 to Week 12 after administration of the investigational product
• Proportion of subjects with amenorrhoea (a total PBAC score of 0) for 6 weeks prior to the end of the investigational product administration
• Time to amenorrhoea (a total PBAC score of 0)
• Proportion of subjects with the maximum NRS score for pain symptoms of ≤1 every 28 days
• Proportion of subjects with the maximum NRS score for pain symptoms of 0 for 28 days prior to the end of the investigational product administration
• Proportion of subjects with the maximum NRS score for pain symptoms of 0 every 28 days
• Mean NRS score for pain symptoms during 28 days prior to the end of the investigational product administration
• Mean NRS score for pain symptoms every 28 days
• Proportion of days without symptoms for 28 days prior to the end of the investigational product administration (days with an NRS score for pain symptoms of 0)
• Proportion of days without symptoms every 28 days (days with an NRS score for pain symptoms of 0)
• Proportion of days with analgesic use for 28 days prior to the end of the investigational product administration
• Proportion of days with analgesic use every 28 days
• Change from baseline in blood hemoglobin, blood hematocrit, serum iron, and serum ferritin at each assessment point
• Percent change from baseline in myoma volume at each assessment point
• Percent change from baseline in uterine volume at each assessment point
• Change from baseline in Uterine Fibroid Symptom (UFS)-QOL scores at each assessment point
• Proportion of general symptoms in Patient Global Impression of Change (PGIC) at the last assessment in the treatment period
• Incidence of adverse events and adverse drug reactions
• Change and variability from baseline in clinical laboratory tests (hematology, blood biochemistry, and urinalysis) at each assessment point
• Change and variability from baseline in vital signs (blood pressure, pulse rate, and body temperature) at each assessment point
• Change and variability from baseline in body weight at each assessment point
• Change and variability from baseline in 12-lead electrocardiogram (ECG) parameters at each assessment point
• Duration from last dose of the investigational product to menstrual recovery
• Plasma concentrations of KLH-2109 (unchanged drug) and KP017 (major metabolite) at each assessment point

• Change from baseline of estradiol (E2), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and progesterone at each assessment point

Study population:

1. Inclusion criteria

<u>At the time of obtaining informed consent</u>

1) Japanese patients who give written informed consent to participate in this study (all relatives within the second degree of kinship are Japanese)
2) Premenopausal women aged 20 years or older (at the time of informed consent)
3) Patients who are available for outpatient visits throughout the study period
4) Patients who are able to record a symptom diary as instructed by the investigator, subinvestigator, or study collaborators
5) Patients diagnosed by transvaginal ultrasound, abdominal ultrasound, MRI, CT, or laparoscopy to have uterine fibroids by the time of informed consent

<u>At the start of the screening period</u>

6) Patients confirmed by transvaginal ultrasonography at the start of the screening period to have at least one myoma that meets all of the following criteria:
   – 3 cm or longer in the longest diameter
   – Not presenting calcification
   – Not receiving surgical treatment
7) Patients with a normal menstrual cycle (25 to 38 days between the start date of a menstruation and the day before the start of the next menstruation) immediately before the start of the screening period and with at least 3 consecutive menstrual days with bleeding that are confirmed during the menstrual cycle

<u>At the start of the run-in period</u>

8) Patients with a normal menstrual cycle (25 to 38 days) immediately before the start of the run-in period and with at least 3 consecutive menstrual days with bleeding that are confirmed during the menstrual cycle (at least 2 menstrual cycles in total for inclusion criteria 7) and 8))

<u>At the start of the treatment period</u>

9) Patients confirmed by transvaginal ultrasonography at the start of the treatment period to have at least one myoma that meets all of the following criteria (same myoma as one measured in the inclusion criterion 6)):
   – 3 cm or longer in the longest diameter
   – Not presenting calcification
   – Not receiving surgical treatment
10) Patients with a normal menstrual cycle (25 to 38 days) immediately before the start of the treatment period and with at least 3 consecutive menstrual days with bleeding that are confirmed during the menstrual cycle (at least 3 menstrual cycles in total for inclusion criteria 7), 8), and 10))
11) Patients who have an input rate of PBAC scores (bleeding or not) into the symptom diary of ≥75% in a single menstrual cycle immediately before the start of the treatment period
12) Patients who have an input rate of NRS scores into the symptom diary of ≥75% in a single menstrual cycle immediately before the start of the treatment period
13) Patients diagnosed with menorrhagia with a total PBAC score of ≥120 in a single menstrual cycle immediately before the start of the treatment period
14) Patients with the maximum NRS score for pain symptoms of uterine fibroid of ≥4 in a single menstrual cycle immediately before the start of the treatment period
15) Patients with an NRS score for pain symptoms of uterine fibroids of ≥1 for at least 2 days in a single menstrual cycle immediately before the start of the treatment period

2. Exclusion criteria

1) Patients with a concurrent or past history of hematologic diseases (including thalassemia, sickle cell anaemia, folate deficiency, and coagulopathy) (excluding iron deficiency anaemia and latent iron deficiency anaemia)
2) Patients with a history of severe hypersensitivity or severe allergy to sanitary products
3) Patients with abdominal pain lower due to irritable bowel syndrome or severe cystitis interstitial
4) Patients with concurrent pelvic inflammatory disease or a history of pelvic inflammatory disease within 8 weeks before the start of the screening period
5) Patients with a history of total hysterectomy or bilateral oophorectomy
6) Patients with concomitant thyroid dysfunction accompanied by menstruation irregular or those who are judged by the investigator or subinvestigator to have the possibility of menstruation irregular due to thyroid dysfunction
7) Patients who are judged by the investigator or subinvestigator to have significant metrorrhagia or significant bleeding anovulatory
8) Patients with concurrent abnormal genital haemorrhage that cannot be diagnosed
9) Patients who have used anticoagulants, antiplatelet drugs, tranexamic acid, or selective estrogen-receptor modulators within 4 weeks before the start of the run-in period (excluding topical preparations and dietary supplements)
10) Patients who have used oral contraceptives or sex hormones (norethindrone, norethisterone, medroxyprogesterone, estrogen, or other progestins) within 8 weeks before the start of the run-in period
11) Patients who have received gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists, dienogest, danazol, or aromatase inhibitors within 16 weeks before the start of the run-in period (patients treated with the extended-release formulation follow the exclusion criteria 12) and 13))
12) Patients who received a 4-week extended-release formulation of a GnRH agonist or GnRH antagonist within 20 weeks before the start of the run-in period

13) Patients who have received a long-term sustained release formulation for 12-week or 3-month of a GnRH agonist or GnRH antagonist within 28 weeks before the start of the run-in period
14) Patients who have received drugs that prolong the QT/QTc interval at the start of the screening period
15) Patients with a complication of clinically significant cardiovascular disease (including myocardial infarction and angina unstable that occurred within 24 weeks before the start of the screening period)
16) Patients with a history of risk factors for Torsades de pointes (including heart failure, hypokalemia, and a family history of long QT syndrome)
17) Patients with any of the following in 12-lead ECG at the start of the screening, run-in, or treatment period:
– Abnormal ECG findings of clinical concern
– QTc interval > 470 msec
18) Patients with any of the following measurements of blood pressure at the start of the screening, run-in, or treatment period:
– Systolic blood pressure ≥ 180 mmHg
– Diastolic blood pressure ≥ 110 mmHg
19) Patients with any of the following measurements of clinical laboratory tests at the start of the screening or run-in period:
– Blood hemoglobin concentration < 8 g/dL
– Any of alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin, ≥ 2 × the upper limit of normal (ULN)
– Serum creatinine ≥ 2.0 mg/dL
20) Patients with positive* results of cervical cytology performed within 1 year before the start of the screening period (if no test results are available, cervical cytology should be performed to obtain the results by the start of the treatment period)
* "Positive" is defined as cases other than Class I or II in the classification by Japan Association of Obstetricians and Gynecologists or cases other than Negative for intraepithelial lesion of malignancy (NILM) in the Bethesda system classification.
21) Patients with a concurrent or past history of active liver disorder or jaundice
22) Patients with concurrent malignant tumor or with a history of malignant tumor within 5 years before informed consent
23) Patients with a concurrent or past history of any of the following diseases which severity is severe and who are considered unsuitable for the study by the investigator or subinvestigator:
– Renal disorders, cardiovascular diseases, endocrine diseases, metabolic diseases, pulmonary diseases, gastrointestinal diseases, neurological diseases, urological diseases, immune diseases
24) Patients with a concurrent or past history of hypersensitivity (including allergy) to synthetic GnRH, GnRH agonists, or GnRH antagonists
25) Patients with a history of severe drug hypersensitivity (including anaphylactic shock)
26) Patients with a concurrent or past history of drug abuse (defined as illegal use of drugs)
27) Patients with a concurrent or past history of alcoholism
28) Patients with psychiatric diseases (especially depression-like symptoms) or suicide attempts attributable to psychiatric diseases and who are considered unsuitable for the study by the investigator or subinvestigator
29) Patients who are pregnant or breastfeeding, who wish to become pregnant during the study period, or who are not willing to use contraception in an appropriate manner
30) Patients who received another investigational product within 24 weeks before informed consent
31) Patients who have previously received KLH-2109 (including placebo)
32) Patients who failed to screen after re-enrollment
33) Other than the above, patients considered unsuitable for the study by the investigator or subinvestigator

Study design:

A placebo-controlled, multicenter, randomized, double-blind, parallel-group comparative study

Investigational product:

• KLH-2109 Tablets 100 mg: A pale yellow film-coated tablet containing 100 mg of KLH-2109 free form in a tablet
• KLH-2109 Tablets placebo: A pale yellow film-coated tablet containing 0 mg of KLH-2109 in a tablet

Dosage and administration:

1. Screening period

The investigational products will not be administered.

2. Run-in period

Two tablets of KLH-2109 placebo will be orally administered once daily (in the morning whenever possible) in a single-blind manner. Administration will be initiated from the visit at the start of the run-in period (Visit 2) until the day before the visit at the start of the treatment period (Visit 3). The investigational drug will be administered at the study site after various tests on the visit at the start of the run-in period.

3. Treatment period

Two tablets of KLH-2109 100 mg or KLH-2109 placebo will be orally administered once daily (in the morning whenever possible) for 12 weeks in a double-blind manner.

Administration will be initiated from the visit at the start of the treatment period (Visit 3) until the day before the visit at Week 12 of the treatment period (Visit 6) The investigational drug will be administered at the study site after various tests except for tests after administration of the investigational drug on the visit at the start of the treatment period. At the visits of Weeks 4 and 8 of the treatment period (Visits 4 and 5), subjects will visit the study site without taking the investigational product for the treatment period, and the investigational product will be administered after various tests.

4. Follow-up period
The investigational products will not be administered.

Concomitant treatment:

1. Oral iron preparation

If an oral iron preparation is not used at the start of the screening period and hemoglobin is <10 g/dL at the start of the screening period, an oral iron preparation of 100 mg/day should be used from the start of the run-in period to the end of the treatment period (or discontinuation).

If an oral iron preparation has been used since before the start of the screening period, the dosage regimen should not be changed until the end of the treatment period (or discontinuation).

However, the use of an oral iron preparation may be discontinued in case that the investigator or subinvestigator judges that the use is not necessary due to the occurrence of adverse events, etc.

2. Analgesic drugs

From the start of the screening period to the end of the treatment period (or discontinuation), analgesic drugs may be used if any of the following is applicable:

• When subjects have severe pain associated with uterine fibroids
• When treatment for adverse events is required

When analgesic drugs are used for severe pain associated with uterine fibroids, the drug and dosage regimen should not be changed to the extent possible. The use of analgesic drugs to prevent pain associated with uterine fibroids and adverse events is not allowed.

Analgesic drugs used for treatment of complications since before the start of the screening period should be used without changing the drug and dosage regimen to the extent possible until the end of the follow-up period.

3. Prohibited concomitant mediations

The use of the following drugs is prohibited from the start of the screening period to the end of the follow-up period.

Category	Names of main drugs
1) GnRH agonist	Buserelin acetate, nafarelin acetate, leuprorelin acetate, goserelin acetate, etc.
2) GnRH antagonist	Cetrorelix acetate, ganirelix, degarelix, relugolix, etc.
3) Hormone drugs mainly composed of LH or estrogen, combination drug of LH and estrogen	Dienogest, Lunabell combination drug, Yaz combination drug, Jemina combination tablet, other hormone drugs (including progesterone, neuroendocrine tumor [NET], norgestrel and chlormadinone acetate), medium-dose pills, low-dose pills, etc.
4) Testosterone derivatives	Danazol, etc.
5) Selective estrogen-receptor modulators (SERMs)	Tamoxifen citrate, raloxifene hydrochloride, bazedoxifene acetate, etc.
6) Aromatase inhibitors	Anastrozole, exemestane, and letrozole, etc.
7) Chinese herbal medicine used to improve menstruation-related symptoms	Shakuyakukanzoto, Keishibukuryogan, Tokishakuyakusan, Tokakujokito, etc.
8) Corticosteroid preparation*	Cortisone, prednisolone, methylprednisolone, triamcinolone, dexamethasone, betamethasone, etc.
9) Anticoagulants, antiplatelets, tranexamic acid	Warfarin, heparin, antithrombin drugs, factor Xa inhibitors, aspirin, ticlopidine, clopidogrel, cilostazol, limaprost, Transamin, tranexamic acid capsules, etc.
10) Anaemia drug	Iron preparation (injection), vitamin B12, vitamin B6, folic acid, etc.
11) Antiepileptics, anticonvulsants, antidepressants, antipsychotics, ergot alkaloids	Phenytoin, sodium valproate, paroxetine, duloxetine, mirtazapine, haloperidol, chlorpromazine, risperidone, olanzapine, ergotamine, methylergometrine, etc.
12) Drugs known to cause QT prolongation*	Quinidine, disopyramide, procainamide, cibenzoline, flecainide, sotalol, nifekalant, amiodarone, bepridil, macrolide antibiotics, new quinolone antibiotics, sulfamethoxazole and trimethoprim (ST) combination drug, itraconazole, hydroxyzine, probucol, haloperidol, chlorpromazine, imipramine, amitriptyline, famotidine, sulpiride, domperidone, doxorubicin, etc.
13) CYP2C8 substrates (limited to drugs that are susceptible to drug interactions and have a narrow therapeutic window)	Repaglinide, paclitaxel, sorafenib, etc.
14) Investigational products other than KLH-2109	Various investigational products

* Excluding topical application

4. Prohibited concomitant therapy

The use of the following concomitant therapy is prohibited from the start of the screening period to the end of the follow-up period.

• Surgical treatment for uterine fibroids
• Other concomitant therapy that may affect the efficacy evaluation

5. Other concomitant treatment

Drugs used for treatment of complications at the start of the screening period should be used without changing the dosage regimen to the extent possible until the end of the follow-up period. Concomitant therapy for treatment of complications conducted since before the start of the screening period should not be changed to the extent possible until the end of the follow-up period. No new concomitant medications or therapies should be initiated during the study period. However, concomitant medications and therapies should be initiated in case that the investigator or subinvestigator judges that they are necessary due to the occurrence of adverse events, etc. The dosage regimen of the concomitant drugs and concomitant therapies are allowed to be changed.

Investigation, observation, examination, evaluation items, and timing: Refer to the schedule of activities.
Sample size: A total of 78 subjects will be included in the study, which is composed of 39 subjects per group (KLH-2109 200 mg group and placebo group).

Schedule of activities

		Screening period	Run-in period	Treatment period				Follow-up period
Visit		1	2	3	4	5	6	7
Weeks after administration		—	—	(Start of treatment period)	Week 4	Week 8	Week 12 (or discontinuation)	Week 16 (Week 4 of Follow-up period)
Days after administration [a)]		Day −118 to −26	Day −42 to −21 [b)]	1[b)]	29	57	85	—
Visit windows (day)					±4	±7	±7	±7
Informed consent [c)]		X						
Subject demographic		X	X	X				
Confirmation of eligibility		X	X	X				
Registration		Tentative registration [d)]	Tentative registration	Main registration				
Symptom diary recording [e)]		X	→	→	→	→	→	
Confirmation of compliance				X	X	X	X	
UFS-QOL				X			X	
PGIC							X	
Adverse events		X	→	→	→	→	→	X
Confirmation of concomitant medications and therapies		X	→	→	→	→	→	X
12-lead ECG	Before administration of the investigational product	X	X	X	X	X	X	X
	After administration of the investigational product			X[f)]				
Vital signs		X	X	X	X	X	X	X
Body weight		X	X	X	X	X	X	X
Clinical laboratory tests		X	X	X	X	X	X	X
Pregnancy test		X	X	X	X	X	X	X
Pharmacodynamic tests				X	X	X	X	X
Pharmacokinetics				X[f)]	X	X	X	
Myoma volume and uterine volume		X[g)]		X	X	X	X	
Prescription of the investigational product for the run-in period			X					
Prescription of the investigational product for the treatment period				X	X	X		
Confirmation of the start date of menstruation			X	X				X[h)]

a) The first day of administration of the investigational product for the treatment period is Day 1, and the day before the first day of administration is Day −1.
b) It should be performed during Days 1 to 5 of menstruation.
c) The written informed consent must be obtained by the start of the screening period (before performing the tests specified in this study). In addition to Day −118 to Day −26, informed consent may be obtained before Day −118.
d) Subjects will be tentatively registered at the time of obtaining informed consent and the start of the screening period.
e) The PBAC score, NRS score, and analgesic use will be recorded from the visit at the start of the screening period to the day before the visit at Week 12 of the treatment period.
f) It should be performed 3 hours after administration of the investigational product for the treatment period (acceptable range ± 30 minutes).
g) Only when transvaginal ultrasonography is performed before informed consent and informed consent is obtained and the screening period starts on the same day, the result of transvaginal ultrasonography may be used as data at the start of the screening period.
h) The start date of the first menstruation after the last dose of the investigational product for the treatment period will be determined based on the subjects' interview.

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List of abbreviations and definitions of terms

Abbreviations and terms	Definitions
E2	Estradiol
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
IWRS	Interactive Web Response System
LH	Luteinizing hormone
NET	Norethisterone
NILM	Negative for Intraepithelial Lesion or Malignancy
NRS	Numerical Rating Scale
PBAC	Pictorial Blood Loss Assessment Chart
PGIC	Patient Global Impression of Change
QOL	Quality of Life
SERMs	Selective estrogen-receptor modulator
ST combination drug	Combination drug of sulfamethoxazole and trimethoprim
UFS-QOL	Uterine Fibroid Symptom and Quality of Life

1. History and Background of the Clinical Study Plan

1.1 Uterine fibroids

A uterine fibroid is a benign tumor that occurs in the smooth muscles that make up the myometrium, grows in a sex hormone-dependent manner (estrogen and progesterone), and is the most frequent gynecologic oncologic disease[1)]. Representative symptoms of uterine fibroids include menorrhagia and associated anaemia, dysmenorrhoea, pressure symptoms, pain, and infertility. In addition, symptoms of menorrhagia and chronic pain symptoms during or outside the menstrual period have a significant impact on a patient's QOL[2)].

1.2 Treatment of uterine fibroids

The treatment strategy for uterine fibroids is determined by the presence or absence of symptoms and the desire to have a baby or to preserve the uterus. Asymptomatic uterine fibroid is not treated but followed up. Symptomatic uterine fibroids will be treated with pharmacotherapy or surgical therapy according to symptoms. For patients who wish to preserve the uterus, minimally invasive therapy such as medical therapy, uterine artery embolization (UAE), and MR-guided focused ultrasound (MRgFUS) or uterine myomectomy are performed. Total hysterectomy is the definitive treatment for uterine fibroid in subjects who do not wish to have children or conserve the uterus [3),4)].

Pharmacotherapy for uterine fibroid includes symptomatic treatment and endocrine therapy. As symptomatic treatment, tranexamic acid and iron preparation are generally administered for menorrhagia, and anti-inflammatory analgesics and Chinese medicines are administered for dysmenorrhoea. In the endocrine therapy, GnRH agonists are widely used and can reduce the size of uterine fibroids and improve its symptoms. Therefore, they are used to reduce the risk of surgery and invasiveness caused by conversion (conservative treatment until surgery of patients eligible for surgery) or to avoid surgery temporarily or until menopause (conservative treatment until menopause) [3),4)]. On the other hand, GnRH agonists have been noted to cause decreased bone mineral content resulting from a hypoestrogenic state, temporary worsening of symptoms due to flare-up in the early phase of treatment, and prolonged time to respond to the treatment. It also requires a long time to recover GnRH sensitivity after completion/discontinuation of treatment, and consequently, it takes a long time to resolve adverse drug reactions resulting in hypoestrogenic symptoms and recover menstruation. In addition, only injectable or nasal GnRH agonists are currently on the market, and issues related to the dosage form have been pointed out[1)]. Relugolix, a GnRH antagonist, was approved in January 2019 for the indication of improving various symptoms associated with uterine fibroids (menorrhagia, abdominal pain lower, lumbago, and anaemia).

1.3 Background of development of KLH-2109

KLH-2109 is a small-molecule compound newly created by Kissei Pharmaceutical Co., Ltd., and is a nonpeptidic GnRH antagonist that can be orally administered. KLH-2109 acts directly on GnRH receptors in the pituitary gland and reduces estrogen levels through the inhibition of gonadotropin secretion by antagonism of GnRH receptors, thereby improving symptoms such as endometriosis and

uterine fibroids, which are sex hormone-dependent diseases.

The development for uterine fibroids outside Japan is ongoing by ObsEva. Two foreign phase III clinical studies in patients with uterine fibroids (16-OBE2109-008 and 16-OBE2109-009) confirmed that KLH-2109 inhibited E2 in a dose-dependent manner, improved various symptoms associated with uterine fibroids (menorrhagia, pain symptoms, and anaemia), and reduced uterine volume and myoma volume. Treatment with KLH-2109 is expected to improve symptoms associated with uterine fibroids.

1.3.1 Nonclinical study results

The following nonclinical studies were conducted with KLH-2109 choline. All doses and concentrations represent those of KLH-2109 free form.

1.3.1.1 Pharmacology studies

In the primary pharmacodynamics studies, KLH-2109 showed high affinity for human, monkey, and rat GnRH receptors with a Ki value of 27.4, 75.2, and 274 nmol/L, respectively. Furthermore, KLH-2109 antagonized human GnRH receptors in concentration-dependent manner with an IC_{50} of 36.7 nmol/L.

KLH-2109 choline reduced significantly LH secretion in male rats induced by leuprolide, and the effect persisted in a dose-dependent manner. In addition, serum LH levels were continuously reduced in castrated male monkeys. Furthermore, KLH-2109 choline inhibited E2 secretion in proestrous female rats in a dose-dependent manner, confirming its inhibitory effect on LH and estrogen secretion. In a rat model of endometriosis, KLH-2109 choline reduced the cyst volume at the implantation site of endometrial sections. These results suggest that KLH-2109 choline suppresses LH secretion and decreases estrogen secretion through antagonistic action of GnRH receptors and ameliorates endometriosis and uterine fibroids by lesion atrophy or the suppression of endometrial proliferation.

KP017, a major metabolite of KLH-2109 in human hepatocytes, had a lower affinity for human GnRH receptors than KLH-2109.

Secondary pharmacological studies showed little binding of KLH-2109 to various receptors, channels, and transporters (75 types).

In the safety pharmacological studies, KLH-2109 choline did not affect the central nervous system of female rats in a single oral dose at up to 2000 mg/kg. KLH-2109 choline also did not affect body temperature, respiratory system, and cardiovascular system of female monkeys in a single oral dose at up to 1000 mg/kg. In addition, KLH-2109 choline at up to 100 μmol/L had no effect on both potassium current through hERG channel expressed in HEK293 cells (hERG current) and action potential parameters in papillary muscle isolated from guinea pigs. These results suggest that KLH-2109 choline is a well-tolerated drug in clinical use.

1.3.1.2 Pharmacokinetics studies

After single oral dose of KLH-2109 choline to rats (1, 3, 10, and 30 mg/kg) and monkeys (3 mg/kg), KLH-2109 was rapidly absorbed, reaching C_{max} within 1.5 and 2 hours after administration, respectively. Thereafter, KLH-2109 choline gradually disappeared with a $t_{1/2}$ of 9.9 to 14.3 hours and 7.4 hours, respectively. In rats, C_{max} and $AUC_{0-\infty}$ of KLH-2109 increased almost in a dose-dependent manner, and KLH-2109 appeared to show linear kinetics within the dose range. [^{14}C]KLH-2109 was extensively

absorbed in the gastrointestinal tract, with especially good absorption from duodenum and jejunum. Bioavailability was at least 80% in rats and monkeys.

The volume of distribution at steady state (Vd_{ss}) of KLH-2109 was approximately ≤0.3 L/kg. Distribution studies and blood cell distribution studies also showed low transfer to tissues and blood cells. Furthermore, radioactivity concentrations in the cerebrum and cerebellum were ≤0.03 times those in plasma/blood, suggesting that transfer of KLH-2109 to brain is low. One of the factors for the low transfer to tissues may be the high protein binding rate of KLH-2109 of ≥99%. Radioactivity concentrations in tissues, including melanin-containing tissues, decreased in the same manner as radioactivity levels in plasma/blood, suggesting that KLH-2109 was unlikely to persist in tissues. Radioactivity concentrations in fetuses gradually increased relative to that in mothers and reached the peak at ≥48 hours post-dose, suggesting that KLH-2109 and its metabolites penetrate the placenta and are slowly distributed to fetuses.

KLH-2109 was mainly present in the plasma of mice, rats, and monkeys. KLH-2109 was also mainly detected in the pituitary gland (rat), which is the site of action. Major metabolites detected in other biological samples included KP017 (*O*-demethylation), KP018 (*O*-dealkylation), and KP046 (*O*-demethylation) in mice and monkeys. In mice, KP049 (sulfate conjugate of KP018), KP050 (glucuronide conjugate of KP017), and KP143 (glucuronide conjugate of KP046) were detected. In rats, KP018 and KP048 (sulfate conjugate of KP046) were detected, and KP017 was also slightly detected. In human hepatocytes, KP017 and KP050 were the major metabolites. In human liver microsomes, KP017, KP018, and KP046 were formed in the presence of nicotinamide adenine dinucleotide phosphate (NADPH), and KP017 seemed to be formed mainly by CYP2C9 and KP046 may be formed mainly by cytochrome (CYP) 2C8, 2C9, and 3A4. KP018 was suggested to be formed nonenzymatically from KP046 at physiological pH, as well as to be generated by CYP1A2, 2B6, and 2D6.

After a single oral dose of [^{14}C]KLH-2109 choline to rats and monkeys, approximately 70% of the administered radioactivity was excreted in feces. In bile duct-cannulated rats, approximately 87% of the administered radioactivity was absorbed and approximately 60% was excreted in the bile, suggesting that the main route of excretion of KLH-2109 was via the bile in feces. KLH-2109 may circulate enterohepatically because it was present mainly as KLH-2109 in bile and approximately 80% of the radioactivity excreted in bile was reabsorbed. In lactating rats, radioactivity in plasma was gradually transferred into milk, but the $AUC_{0-\infty}$ ratio was small, indicating that the transfer of KLH-2109 and its metabolites was low.

Pharmacokinetic drug interactions with representative nonsteroidal anti-inflammatory drugs were evaluated in *in vitro* studies. As a result, KLH-2109 was considered unlikely to cause interactions attributable to these nonsteroidal anti-inflammatory drugs and plasma protein binding. KLH-2109 demonstrated direct and time-dependent inhibition of CYP2C8 activity and induction of CYP3A4/5 activity at high concentrations. As for the major drug transporters, KLH-2109 was shown to be a substrate of organic anion transport polypeptide (OATP)1B1, OATP1B3, and organic anion transporter (OAT)3, suggesting that KLH-2109 inhibits OAT3-mediated drug transport. KLH-2109 was considered unlikely to be a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), OAT1,

organic cation transporter (OCT)2, multidrug and toxin extrusion (MATE)1, and MATE2-K and unlikely to affect drug transport via P-gp, BCRP, MATE1, and MATE2-K. KLH-2109 was unlikely to cause drug interactions and drug-induced liver disorder due to bile salt export pump (BSEP) inhibition.

1.3.1.3 Toxicity study

In a 4-week oral dose toxicity study in rats at doses up to 2000 mg/kg/day; a 13-week oral dose toxicity study in rats at doses up to 1500 mg/kg/day; a 26-week oral dose toxicity study in rats at doses up to 1000 mg/kg/day; 4-, 13-, and 39-week oral dose toxicity study in monkeys at doses up to 1000 mg/kg/day; a 4-week oral dose toxicity study in dogs at doses up to 1000 mg/kg/day; and a 13-week oral dose toxicity study in mice at doses up to 1500 mg/kg/day, no serious toxicity was observed except for death in mice at 1500 mg/kg/day. Atrophy of reproductive organs and tissues, which is considered to be due to the pharmacological action of KLH-2109 choline as a GnRH receptor antagonist, was mainly observed. These atrophies were consistent throughout the treatment period and reversible. In the 4-week study, the no-observed-adverse-effect levels (NOAELs) were determined to be 200 mg/kg/day in rats, 100 mg/kg/day in monkeys, and 100 mg/kg/day in dogs, because body weight increased, red blood cell count decreased, and renal tubular disorder were observed in female rats at 2000 mg/kg/day, and slight increases in serum hepatic enzymes (up to 4.7 times the baseline level) without histological changes in the liver were observed in female monkeys at 1000 mg/kg/day, as well as slight increases in serum hepatic enzymes (up to 4.0 times the baseline level) and dark granules in the gallbladder were observed in female dogs at 1000 mg/kg/day. In the 13-week study, the NOAELs were determined to be 500 mg/kg/day in rats, 10 mg/kg/day in monkeys, and 40 mg/kg/day in mice, because body weight increased, thyroid follicular dilation suggestive of mild decreased thyroid hormone synthesis and mild renal tubular damage were observed in female rats at 1500 mg/kg/day, and mild increases in serum hepatic enzymes (up to 2.2 times the baseline level) without histological changes in the liver were observed in female monkeys at ≥100 mg/kg/day, as well as biliary sand in the gallbladder and renal tubular damage were observed in female mice at ≥750 mg/kg/day. In the 26-week study in rats, the NOAEL was determined to be 200 mg/kg/day because body weight increased and mild thyroid follicular dilation were observed in females at 1000 mg/kg/day. In the 39-week study in monkeys, the NOAEL was determined to be 10 mg/kg/day, because slight increases in serum hepatic enzymes (up to 5.0 times the baseline level) were observed in females at ≥100 mg/kg/day.

The renal findings observed in rats and mice were considered to be rodent-specific changes. Furthermore, when the exposure at the NOAEL in the 13-week rat study ($AUC_{0\text{-}24hr}$, 4350000 ng•hr/mL) and the 13-week mouse study ($AUC_{0\text{-}24hr}$, 2090000 ng•hr/mL) were compared with that at 200 mg/day in healthy premenopausal Japanese women for 7 days in the phase I study (AUC_{τ}, 412144.6 ng•hr/mL), the 11- and 5-times safety margins were obtained, respectively. Therefore, safety concerns in the phase III clinical study (Study KLH2301, dose 200 mg/day) were considered to be low. The thyroid findings observed only in rats were considered to be specific to rats. Furthermore, when the exposure at the NOAEL in the 26-week rat study ($AUC_{0\text{-}24hr}$, 2700000 ng•hr/mL) was compared with that at 200 mg/day in healthy premenopausal Japanese women for 7 days in the phase I study (AUC_{τ}, 412144.6 ng•hr/mL),

the 7-times safety margin was obtained. Therefore, safety concerns in the phase III clinical study were considered to be low. Regarding increases in serum hepatic enzymes in monkeys, when the exposure at the NOAEL of 10 mg/kg/day in the 13- and 39-week monkey studies ($AUC_{0\text{-}24hr}$, 282000 ng•hr/mL in the 13-week study and 310000 ng•hr/mL in the 39-week study) was compared with that at 200 mg/day in healthy premenopausal Japanese women for 7 days in the phase I study (AUC_{τ}, 412144.6 ng•hr/mL), the safety margin was not sufficient. However, in the 39-week study in monkeys, no histopathological changes suggesting hepatotoxicity were observed even at 1000 mg/kg/day, which was 7-times the exposure in humans at 200 mg/day for 7 days ($AUC_{0\text{-}24hr}$, 2910000 ng•hr/mL), and the increase in serum hepatic enzymes was reversible. In a 4-week study in dogs, a nonrodent species different from monkeys, the potential for hepatotoxicity was investigated. As in monkeys, increases in serum hepatic enzymes were observed but were not accompanied by histopathological changes. Changes described above did not appear to interfere with the conduct of the phase III clinical studies. A mechanistic study was conducted for dark granules in the gallbladder in the 4-week study in dogs and biliary sand in the gallbladder in the 13-week study using mice. The results suggested that the mechanisms of development of these findings were attributable to the precipitation of KLH-2109 resulting from its concentration in bile exceeding its solubility. In the mechanistic study in dogs, similar deposits were observed in the gallbladder of some animals at 100 mg/kg/day, which was the NOAEL in the 4-week toxicity study in dogs, and the KLH-2109 concentration in bile at this dose exceeded its solubility in bile. In the phase I study, the maximum concentration of KLH-2109 in bile estimated from the blood exposure in healthy premenopausal Japanese women receiving 200 mg/day for 7 days was 4.3% to 5.7% of the mean solubility of KLH-2109 in human bile. Therefore, the gallbladder findings observed in dogs and mice do not suggest the occurrence in humans and were not considered to interfere with the conduct of the phase III clinical studies. This finding was not observed in the highest dose group (1000 mg/kg/day) in the 13- and 39-week studies in monkeys.

In genotoxicity studies, KLH-2109 choline was not genotoxic.

In carcinogenicity studies, KLH-2109 choline was not carcinogenic after oral administration to rats for 2 years and Tg rasH2 mice for 26 weeks.

In a study on female fertility and early embryonic development, KLH-2109 choline was orally administered to female rats prior to pregnancy for 30 days. As the findings attributable to the pharmacological action of KLH-2109 choline, effects on the estrous cycle and number of implantations at 20 and 100 mg/kg/day and effects on the conception rate at 100 mg/kg/day were observed. The findings at the high dose of 100 mg/kg/day were reversible after a 30-day recovery period, suggesting that KLH-2109 choline was not considered to have an irreversible effect on female reproductive function. When KLH-2109 choline was administered to female rats in the early stage of pregnancy, no effect on embryonic development was observed up to 300 mg/kg/day, but reduction in size of conceptus was observed at 1000 mg/kg/day. No teratogenicity was observed in any of species after administration of KLH-2109 choline to female rats and female rabbits during organogenesis. However, embryonic and fetal deaths tended to increase in association with the occurrence of total embryonic deaths in rat dams at 300 mg/kg/day, and most rabbits did not become pregnant at 30 mg/kg/day. As a result of administration

of KLH-2109 choline to rat dams during pregnancy and lactation period, a tendency of low birth rate was observed at 300 mg/kg/day, which was associated with the occurrence of total embryonic deaths in dams. These findings on embryonic and fetal development in rats and rabbits may be due to the pharmacological action of KLH-2109 choline. Therefore, it was considered that the use of KLH-2109 choline should be avoided in pregnant women and women who wish to become pregnant during the study period.

1.3.2 Clinical study results

1.3.2.1 Pharmacokinetics in humans

Pharmacokinetics in humans were evaluated in a total of 9 clinical studies, including a phase I clinical study (KLH1101), a mass balance study (KLH1103), 4 drug interaction studies (16-OBE2109-005, 17-OBE2109-006, 18-OBE2109-006 and 18-OBE2109-007), a study in subjects with hepatic impairment (18-OBE2109-009), a study in subjects with renal impairment (18-OBE2109-010), and a thorough QT/QTc study (17-OBE2109-001).

In Study KLH1101 in healthy Caucasian postmenopausal women, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ following a single oral dose of KLH-2109 under fasting conditions increased in a dose-dependent manner in a dose range of 12.5 to 400 mg. When 100, 200, or 400 mg of KLH-2109 was repeatedly administered for 7 days to healthy Caucasian and Japanese premenopausal women via the oral route, Caucasian premenopausal women showed similar pharmacokinetics to Caucasian postmenopausal women and Japanese premenopausal women showed similar pharmacokinetics to Caucasian premenopausal women. Following a single dose in Japanese premenopausal women under fasting conditions, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of KLH-2109 increased in a dose-dependent manner in the dose range of 100 to 400 mg. The effect of food on the pharmacokinetics of KLH-2109 was considered not to be significant. No accumulation was observed with repeated administration at any dose level, showing linear pharmacokinetics.

Following a single oral dose of 200 mg of [^{14}C]KLH-2109 in healthy Caucasian postmenopausal women in Study KLH1103, most of the radioactivity in plasma was present as KLH-2109 and other metabolites (KP018, KP017, KP143, and HM2) accounted for <10% of the total radioactivity exposure. Following an oral dose of [^{14}C]KLH-2109, the recovery of radioactivity in urine and feces was 51.5% (geometric mean) and 38.4% (geometric mean), respectively.

Drug interaction studies were conducted to evaluate the pharmacokinetics and safety of co-administered CYP3A4 substrate (midazolam), OATP1B1/1B3 inhibitor (rifampicin), CYP2C8 substrate (repaglinide), and OAT3 substrate (benzylpenicillin) with KLH-2109, respectively. As a result of these studies, KLH-2109 was considered to be a weak inhibitor of CYP2C8, and no interaction was observed with other inhibitors or substrate drugs. In Study 16-OBE2109-005, in which CYP3A4 substrate and KLH-2109 were concomitantly administered, the effect of food (high-fat diet) was also investigated. Administration of KLH-2109 under fed conditions resulted in delayed t_{max} (2.75 hours) and decreased C_{max} (18.35%) due to delayed gastric emptying associated with high-fat diet, compared with administration under fasting conditions, but did not affect AUC.

In Study 18-OBE2109-009, a single oral dose of KLH-2109 200 mg was administered to adult women with mild hepatic impairment, moderate hepatic impairment, severe hepatic impairment, and normal hepatic function. The results of the plasma pharmacokinetic parameters of KLH-2109 were that C_{max} (geometric mean) in subjects with mild, moderate, and severe hepatic impairment was 85%, 85%, and 93% of those with normal hepatic function, respectively, and $AUC_{0\text{-}inf}$ (geometric mean) was 89%, 82%, and 121% of those with normal hepatic function, respectively. As for the plasma pharmacokinetic parameters of unbound KLH-2109, C_{max} (geometric mean) in subjects with mild, moderate, and severe hepatic impairment was 83%, 98%, and 222% of those with normal hepatic function, respectively, and $AUC_{0\text{-}inf}$ (geometric mean) was 87%, 94%, and 288% of those with normal hepatic function, respectively.

In Study 18-OBE2109-010, a single oral dose of 200 mg of KLH-2109 was administered to adult women with mild renal impairment, moderate renal impairment, severe renal impairment, end-stage renal disease, and normal renal function. The results of the plasma pharmacokinetic parameters of KLH-2109 were that C_{max} (geometric mean) in subjects with mild, moderate, and severe renal impairment, and end-stage renal disease was 103%, 104%, 100%, and 83% of those with normal renal function, respectively, and $AUC_{0\text{-}inf}$ (geometric mean) was 110%, 119%, 146%, and 122% of those with normal renal function, respectively. As for the plasma pharmacokinetic parameters of unbound KLH-2109, C_{max} (geometric mean) in subjects with mild, moderate, and severe renal impairment, and end-stage renal disease was 113%, 142%, 139%, and 141% of those of subjects with normal renal function, respectively, and $AUC_{0\text{-}inf}$ (geometric mean) was 121%, 162%, 203%, and 210% of those of subjects with normal renal function, respectively.

In Study 17-OBE2109-001 in healthy premenopausal women, C_{max} and $AUC_{0\text{-}t}$ following a single oral dose of 700 mg of KLH-2109 under fasting conditions increased generally in a dose-dependent manner.

1.3.2.2 Efficacy and safety

Of the clinical studies of KLH-2109 conducted to date, 4 studies in patients with endometriosis were conducted in Japan (KLH1201, KLH1202, KLH1203, and KLH1204) and 1 study outside Japan (15-OBE2109-001) and 2 studies in patients with uterine fibroids were conducted outside Japan (16-OBE2109-008 and 16-OBE2109-009).

In the early phase II clinical studies in patients with endometriosis (KLH1201, KLH1202, and KLH1203), efficacy and safety of KLH-2109 was evaluated when 50, 75, 100, 150, or 200 mg was orally administered once daily after breakfast for 8 weeks (Studies KLH1201 and KLH1203) or 12 weeks (Study KLH1202). These studies confirmed that administration of KLH-2109 improved pelvic pain due to endometriosis.

In Study KLH1204, the dose–response relationship of efficacy and safety of KLH-2109 was evaluated when 25, 50, 75, or 100 mg of KLH-2109 was administered orally once daily after breakfast for 12 weeks in 455 patients with endometriosis in a placebo-controlled, double-blind manner (Period I). In addition, the study also investigated the safety and efficacy of oral administration of KLH-2109 for up to Week 24 (Period II). As a result of this study, the adjusted mean change in the mean NRS score for pelvic

pain at the end of Period I, the primary endpoint, was −0.62 in the KLH-2109 25 mg group, −0.65 in the 50 mg group, −1.06 in the 75 mg group, and −1.33 in the 100 mg group, compared with −0.48 in the placebo group, showing a dose-dependent decrease in the mean NRS score for pelvic pain from Week 0. The adjusted mean differences from placebo (two-sided 95% confidence interval [CI]) were −0.14 (−0.44, 0.16) in the KLH-2109 25 mg group, −0.17 (−0.46, 0.12) in the 50 mg group, −0.58 (−0.88, −0.28) in the 75 mg group, and −0.85 (−1.14, −0.56) in the 100 mg group, showing a significant difference from placebo in the ≥75 mg KLH-2109 groups (ANCOVA; $P < 0.001$ for the KLH-2109 75 and 100 mg groups). The mean NRS score for pelvic pain decreased in the KLH-2109 group from Week 4 of the start of the administration and showed a dose-dependent downward trend throughout Periods I and II.

In Study 15-OBE2109-001, the dose-response relationship of efficacy and safety of KLH-2109 was evaluated when 50, 75, 100, or 200 mg of KLH-2109 was administered orally once daily in 328 patients with moderate to severe pain associated with endometriosis in a placebo-controlled, double-blind manner (main study). In addition, the dose-response relationship in efficacy and safety of KLH-2109 was investigated when 50, 75, or 100 mg of KLH-2109 was administered orally once daily for an additional 28 weeks in subjects who completed the entire treatment period (total of 24 weeks) of the main study (extension study). The results of the main study showed that the response rate in the Verbal Rating Scale (VRS) score for pelvic pain at Week 12, the primary endpoint, was significantly higher in the KLH-2109 groups of 75, 100, and 200 mg than in the placebo group. The KLH-2109 75 mg group had the highest response rate, 61.5%, compared with 34.5% in the placebo group.

In Studies 16-OBE2109-008 and 16-OBE2109-009 in 574 and 535 patients with uterine fibroids with severe menstrual bleeding, respectively, the efficacy and safety of oral administration of KLH-2109 100 mg, 100 mg + E2 1 mg/NETA 0.5 mg (ABT [Add-Back Therapy, hormonal replacement therapy]), KLH-2109 200 mg, or 200 mg + ABT once daily for 24 weeks were evaluated in a double-blind, placebo-controlled manner. Then, the investigational product was administered for 28 weeks to evaluate efficacy and safety up to Week 52. As a result of these studies, the response rates for menstrual blood loss at Week 24, the primary endpoint, were 56.4% (53 of 94 subjects) in the KLH-2109 100 mg group, 67.3% (72 of 107 subjects) in the 100 mg + ABT group, 71.4% (75 of 105 subjects) in the 200 mg group, 75.5% (77 of 102 subjects) in the 200 mg + ABT group, and 35.0% (36 of 103 subjects) in the placebo group in Study 16-OBE2109-008 and 56.7% (55 of 97 subjects) in the KLH-2109 100 mg group, 77.2% (78 of 101 subjects) in the 100 mg + ABT group, 77.7% (80 of 103 subjects) in the 200 mg group, 93.9% (92 of 98 subjects) in the 200 mg + ABT group, and 29.4% (30 of 102 subjects) in the placebo group in Study 16-OBE2109-009. Both studies showed significantly higher response rates in all KLH-2109 groups compared with placebo.

KLH-2109 was administered to a total of 1819 patients with endometriosis or uterine fibroids in previous studies. Adverse events observed in these clinical studies were summarized and evaluated. The incidences of adverse events were 70.37% (1280 of 1819 subjects) in the KLH-2109 group and 52.67% (197 of 374 subjects) in the placebo group, and the incidences of adverse drug reactions were 40.30% (733 of 1819 subjects) in the KLH-2109 group and 19.79% (74 of 374 subjects) in the placebo group.

The incidences of deaths, other serious adverse events, and adverse events leading to discontinuation were 0.05% (1 of 1819 subjects) in the KLH-2109 group and 0.00% (0 of 374 subjects) in the placebo group, 3.52% (64 of 1819 subjects) in the KLH-2109 group and 2.14% (8 of 374 subjects) in the placebo group, and 9.51% (173 of 1819 subjects) in the KLH-2109 group and 5.61% (21 of 374 subjects) in the placebo group, respectively. Adverse drug reactions observed in ≥ 2% of subjects in the KLH-2109 group were hot flush, metrorrhagia, headache, menorrhagia, alanine aminotransferase increased, nausea, and aspartate aminotransferase increased.

In Study 17-OBE2109-001, a single oral dose of KLH-2109 200 mg, 700 mg, moxifloxacin 400 mg, or placebo was administered in a double-blind, 4-treatment, 4-period crossover fashion to healthy premenopausal women under fasting conditions. The mean value (two-sided 90% CI) of ΔΔQTcF (difference of placebo corrected change from baseline of QTcF) at 3 hours post-dose in the KLH-2109 200 mg and 700 mg groups was 8.34 (6.44, 10.23) and 9.92 ms (8.03, 11.81), respectively. Both the KLH-2109 200 and 700 mg groups were considered to have a QT prolongation effect because the upper limit of 90% CI exceeded 10 ms at 3 hours post-dose. However, based on the results of the linear mixed effect model analysis of drug concentration and QT interval, categorical analysis, and analysis of ΔΔJ-Tpeakc (difference of placebo corrected change from baseline of J-Tpeak), the clinical significance of the QT prolongation effect was considered to be small.

1.4 Summary of expected adverse drug reactions and benefits

1.4.1 Expected adverse drug reactions

1.4.1.1 Expected adverse drug reactions based on nonclinical study results

In the repeated-dose toxicity studies, atrophy of reproductive organs and tissues was mainly observed due to inhibition of LH and E2, the mechanism of action of KLH-2109. These changes were well recovered and there were no findings suggestive of decreased bone density.

The target organs for toxicity were the kidney and thyroid in rats, the liver in monkeys, the liver and gallbladder in dogs, and the gallbladder and kidney in mice. The findings in the kidneys of rats and mice and in the thyroid gland of rats were considered to be rodent-specific changes. Furthermore, a sufficient safety margin was obtained to ensure the dose and exposure in the phase III clinical study. Therefore, the findings were not considered to pose a safety problem in humans. Regarding increases in serum hepatic enzymes in the repeated-dose toxicity studies in monkeys, when the exposure at the lowest NOAEL of 10 mg/kg/day in monkeys ($AUC_{0\text{-}24hr}$, 282000 ng•hr/mL in the 13-week study and 310000 ng•hr/mL in the 39-week study) was compared with that at 200 mg/day in healthy premenopausal Japanese women for 7 days in the phase I study (AUC_{τ}, 412144.6 ng•hr/mL), the safety margin was not sufficient. However, in the 39-week study in monkeys, no histopathological changes suggesting hepatotoxicity were observed even at 1000 mg/kg/day, which was 7-times the exposure in humans at 200 mg/day for 7 days ($AUC_{0\text{-}24hr}$, 2910000 ng•hr/mL), and the increase in serum hepatic enzymes was reversible. In a 4-week study in dogs, a nonrodent species different from monkeys, the potential for hepatotoxicity was investigated. As in monkeys, increases in serum hepatic enzymes were observed but were not

accompanied by histopathological changes. Based on the above, there would be no problem in conducting the phase III clinical studies by measuring liver function markers (AST, ALT, lactate dehydrogenase [LDH], alkaline phosphatase [ALP] γ-guanosine triphosphate [GTP], and total bilirubin). A mechanistic study was conducted for dark granules in the gallbladder in the 4-week study in dogs and biliary sand in the gallbladder in the 13-week study using mice. The results suggested that these findings were attributed to the precipitation of KLH-2109 concentration in bile beyond its solubility in bile. In the mechanistic study in dogs, similar deposits were observed in the gallbladder of some animals at 100 mg/kg/day, which was the NOAEL in the 4-week toxicity study in dogs, and the KLH-2109 concentration in bile at this dose exceeded its solubility in bile. In the phase I study, the maximum concentration of KLH-2109 in bile estimated from the blood exposure in healthy premenopausal Japanese women receiving 200 mg/day for 7 days was 4.3% to 5.7% of the mean solubility of KLH-2109 in human bile. Gallbladder findings in dogs and mice and serum ALP increased in dogs were observed, but these findings were not observed in monkeys. Based on the above, there would be no problem in conducting the phase III clinical studies by measuring biliary markers (ALP, γ-GTP, and total bilirubin).

In the reproductive toxicity studies, KLH-2109 was administered to female rats prior to pregnancy. As the findings attributable to the pharmacological action of KLH-2109, effects on the estrous cycle and number of implantations at 20 and 100 mg/kg/day and effects on the conception rate at 100 mg/kg/day were observed. When KLH-2109 was administered to female rats in the early stage of pregnancy, reduction in size of conceptus was observed at 1000 mg/kg/day. When KLH-2109 was administered to female rats and female rabbits during organogenesis, embryonic and fetal deaths tended to increase in association with the occurrence of total embryonic deaths in rat dams at 300 mg/kg/day, and most rabbits did not become pregnant at 30 mg/kg/day. As a result of administration of KLH-2109 to rat dams during pregnancy and lactation period, a tendency of low birth rate was observed at 300 mg/kg/day, which was associated with the occurrence of total embryonic deaths in dams. These findings on embryonic and fetal development in rats and rabbits may be due to the pharmacological action of KLH-2109. Therefore, it was considered that the use of KLH-2109 should be avoided in pregnant women and women who wish to become pregnant during the study period.

1.4.1.2 Expected adverse drug reactions based on clinical studies

Of the clinical studies of KLH-2109 conducted to date, 4 studies in patients with endometriosis were conducted in Japan (KLH1201, KLH1202, KLH1203, and KLH1204) and 1 study outside Japan (15-OBE2109-001) and 2 studies in patients with uterine fibroids were conducted outside Japan (16-OBE2109-008 and 16-OBE2109-009).

A total of 1819 subjects received KLH-2109 in these clinical studies. Adverse drug reactions observed in ≥2% of subjects were hot flush, metrorrhagia, headache, menorrhagia, alanine aminotransferase increased, nausea, and aspartate aminotransferase increased.

1.4.1.3 Other expected adverse drug reactions

Other risks expected to occur in clinical studies based on comprehensive assessment of nonclinical studies, clinical studies, and safety information on drugs in the same class are as follows:

- Bone density decreased with long-term administration (>6 months) of KLH-2109 200 mg without ABT

  The use of drugs that lower E2 levels causes bone density decreased due to increased bone resorption in dose- and duration-dependent manner. KLH-2109 200 mg (without ABT) completely inhibited E2 secretion and bone density decreased by 3% to 4% after 24 weeks of treatment was observed (Studies 15-OBE2109-001, 16-OBE2109-008, and 16-OBE2109-009). It has been confirmed that discontinuation of KLH-2109 restores E2 and improves bone density over time.

- Vaginal/uterine haemorrhage

  In patients with uterine fibroids or endometriosis treated with GnRH analogs, uterine haemorrhage-related events are expected to occur due to changes in hormone balance. Caution has been issued against metrorrhagia with similar drugs[5)-8)]. According to the pooled data from studies in patients with KLH-2109, metrorrhagia (9.68% in the KLH-2109 group and 3.21% in the placebo group, respectively), menorrhagia (3.35% and 1.34%), vaginal haemorrhage (1.43% and 0.53%), and uterine haemorrhage (0.38% and 0.00%) occurred more frequently in the KLH-2109 group than in the placebo group.

- Liver enzymes increased

  Increase in liver function test values has been observed with other oral GnRH antagonists[5),9)]. According to the pooled data from studies in patients with KLH-2109, alanine aminotransferase increased (2.53% in the KLH-2109 group and 0.53% in the placebo group, respectively), aspartate aminotransferase increased (2.09% and 0.27%), and gamma-glutamyl transferase increased (1.15% and 0.27%) occurred more frequently in the KLH-2109 group than in the placebo group. There were no subjects applicable to Hy's law.

1.4.2 Expected benefits

The foreign phase III studies in patients with uterine fibroids demonstrated the efficacy of KLH-2109 in menorrhagia and pain symptoms associated with uterine fibroids. Also in this study, KLH-2109 is expected to improve menorrhagia and pain symptoms associated with uterine fibroids.

2. Study Title and Study Phase

2.1 Study title

A Phase III Confirmatory Study of KLH-2109 in Uterine Fibroid Patients with Menorrhagia and Pain

2.2 Study phase

III

3. Objectives and Endpoints

3.1 Objectives and endpoints

	Objectives	Endpoints
Primary	To confirm the superiority of KLH-2109 200 mg orally once daily for 12 weeks to placebo for efficacy against menorrhagia and pain symptoms in uterine fibroid patients with menorrhagia and pain symptoms in a double-blind manner	• Proportion of subjects with a total PBAC score of <10 from Week 6 to Week 12 after administration of the investigational product • Proportion of subjects with the maximum NRS score for pain symptoms of ≤1 for 28 days prior to the end of the investigational product administration
Secondary	To evaluate the improvement in menorrhagia	• Proportion of subjects with a total PBAC score of <10 from Week 2 to Week 6 after administration of the investigational product • Proportion of subjects with a total PBAC score of <10 for 6 weeks prior to the end of the investigational product administration • Time to a total PBAC score of ≤10 • Proportion of subjects with amenorrhoea (a total PBAC score of 0) from Week 2 to Week 6 after administration of the investigational product • Proportion of subjects with amenorrhoea (a total PBAC score of 0) from Week 6 to Week 12 after administration of the investigational product • Proportion of subjects with amenorrhoea (a total PBAC score of 0) for 6 weeks prior to the end of the investigational product administration • Time to amenorrhoea (a total PBAC score

	Objectives	Endpoints
		of 0)
	To evaluate the improvement in pain symptoms associated with uterine fibroids	• Proportion of subjects with the maximum NRS score for pain symptoms of ≤1 every 28 days • Proportion of subjects with the maximum NRS score for pain symptoms of 0 for 28 days prior to the end of the investigational product administration • Proportion of subjects with the maximum NRS score for pain symptoms of 0 every 28 days • Mean NRS score for pain symptoms during 28 days prior to the end of the investigational product administration • Mean NRS score for pain symptoms every 28 days • Proportion of days without symptoms for 28 days prior to the end of the investigational product administration (days with an NRS score for pain symptoms of 0) • Proportion of days without symptoms every 28 days (days with an NRS score for pain symptoms of 0) • Proportion of days with analgesic use for 28 days prior to the end of the investigational product administration • Proportion of days with analgesic use every 28 days
	To evaluate the improvement in anaemia	• Change from baseline in blood hemoglobin, blood hematocrit, serum iron, and serum ferritin at each assessment point
	To evaluate the reduction of myoma volume and uterine volume	• Percent change from baseline in myoma volume at each assessment point • Percent change from baseline in uterine volume at each assessment point
	To evaluate the improvement in QOL associated with uterine fibroids	• Change from baseline in UFS-QOL scores at each assessment point

	Objectives	Endpoints
		• Proportion of general symptoms in PGIC at the last assessment in the treatment period
	To evaluate safety	• Incidence of adverse events and adverse drug reactions • Change and variability from baseline in clinical laboratory tests (hematology, blood biochemistry, and urinalysis) at each assessment point • Change and variability from baseline in vital signs (blood pressure, pulse rate, and body temperature) at each assessment point • Change and variability from baseline in body weight at each assessment point • Change and variability from baseline in 12-lead ECG parameters at each assessment point • Duration from last dose of the investigational product to menstrual recovery
	To evaluate pharmacokinetics	• Plasma concentrations of KLH-2109 (unchanged drug) and KP017 (major metabolite) at each assessment point
	To evaluate pharmacodynamic effect	• Change from baseline of E2, LH, FSH, and progesterone at each assessment point

3.2 Rationale for the primary endpoint

Improvement in menorrhagia and pain symptoms, the main symptoms of uterine fibroids, are to be assessed as the primary endpoint. The endpoint for menorrhagia is focused on “minimal genital haemorrhage” and is defined as the proportion of subjects with a total PBAC score[10] of <10 points that will indicate adequate improvement in the bleeding profile based on menorrhagia status. In consideration of clinical significance for subjects with moderate or severe pain symptoms associated with uterine fibroids, the endpoint for pain symptoms is the proportion of subjects whose maximum NRS score for pain symptoms improve to ≤1.

3.3 Rationale for the secondary endpoints

- The PBAC score, NRS score, and analgesic use are used to assess improvement in menorrhagia and pain symptoms. Blood hemoglobin, blood hematocrit, serum iron and serum ferritin are determined to evaluate the improvement of anaemia. Myoma volume and uterine volume are used to assess

improvement in objective findings and symptoms related to uterine fibroid, and UFS-QOL and PGIC are chosen to evaluate the improvement in QOL related to uterine fibroids.

- In addition to the items commonly used in safety evaluation, the time from the last dose of KLH-2109 to the menstrual recovery is specified because of the possibility of the disappearance of menstruation following administration of the investigational product.
- Plasma concentrations of KLH-2109 (unchanged form) and KP017 (major metabolite) are determined to evaluate the pharmacokinetics of the investigational product in patients with uterine fibroids.
- Evaluation of E2, LH, FSH, and progesterone is included to confirm the pharmacodynamic effects of KLH-2109 in patients with uterine fibroids.

4. Study Population

Uterine fibroid patients with menorrhagia and pain symptoms who meet all of the following inclusion criteria and none of the exclusion criteria will be included.

4.1 Inclusion criteria

Patients should be confirmed that they meet the following inclusion criteria at the time of informed consent, at the start of the screening period, the run-in period, and the treatment period.

4.1.1 Inclusion criteria

Inclusion criteria at the time of informed consent

1) Japanese patients who give written informed consent to participate in this study (all relatives within the second degree of kinship are Japanese)
2) Premenopausal women aged 20 years or older (at the time of informed consent)
3) Patients who are available for outpatient visits throughout the study period
4) Patients who are able to record a symptom diary as instructed by the investigator, subinvestigator, or study collaborators
5) Patients diagnosed by transvaginal ultrasound, abdominal ultrasound, MRI, CT, or laparoscopy to have uterine fibroids by the time of informed consent

Inclusion criteria at the start of the screening period (Visit 1)

6) Patients confirmed by transvaginal ultrasonography at the start of the screening period to have at least one myoma that meets all of the following criteria:
   - 3 cm or longer in the longest diameter
   - Not presenting calcification
   - Not receiving surgical treatment
7) Patients with a normal menstrual cycle (25 to 38 days between the start date of menstruation and the day before the start of the next menstruation) immediately before the start of the screening period and with at least 3 consecutive menstrual days with bleeding that are confirmed during the menstrual cycle

Inclusion criteria at the start of the run-in period (Visit 2)

8) Patients with a normal menstrual cycle (25 to 38 days) immediately before the start of the run-in period and with at least 3 consecutive menstrual days with bleeding that are confirmed during the

menstrual cycle (at least 2 menstrual cycles in total for inclusion criteria 7) and 8))

Inclusion criteria at the start of the treatment period (Visit 3)

9) Patients confirmed by transvaginal ultrasonography at the start of the treatment period to have at least one myoma that meets all of the following criteria (same myoma as one measured in the inclusion criterion 6)):
   - 3 cm or longer in the longest diameter
   - Not presenting calcification
   - Not receiving surgical treatment
10) Patients with a normal menstrual cycle (25 to 38 days) immediately before the start of the treatment period and with at least 3 consecutive menstrual days with bleeding that are confirmed during the menstrual cycle (at least 3 menstrual cycles in total for inclusion criteria 7), 8), and 10))
11) Patients who have an input rate of PBAC scores (bleeding or not) into the symptom diary of ≥75% in a single menstrual cycle immediately before the start of the treatment period
12) Patients who have an input rate of NRS scores into the symptom diary of ≥75% in a single menstrual cycle immediately before the start of the treatment period
13) Patients diagnosed with menorrhagia with a total PBAC score of ≥120 in a single menstrual cycle immediately before the start of the treatment period
14) Patients with the maximum NRS score for pain symptoms of uterine fibroid of ≥4 in a single menstrual cycle immediately before the start of the treatment period
15) Patients with an NRS score for pain symptoms of uterine fibroids of ≥1 for at least 2 days in a single menstrual cycle immediately before the start of the treatment period

4.1.2 Rationale for inclusion criteria

1)	It is set in accordance with the ethical principles of the Declaration of Helsinki and the Good Clinical Practice (GCP).
2)	The age is set at or above the legal age at which consent can be obtained by the patient only. Moreover, only premenopausal patients are included to assess efficacy and safety against uterine fibroids appropriately, because uterine fibroids are estrogen-dependent.
3)	Considering that patients with uterine fibroids are generally treated as outpatients and that changes in the living environment associated with hospitalisation may affect the efficacy evaluation, patients who are able to visit the outpatient clinic are selected.
4), 11), 12)	It is set for the evaluation using the symptom diary.
5), 6), 9)	It is set to confirm that patients have a uterine fibroid which is applicable to the evaluation.
7), 8), 10)	It is set to include patients with normal menstrual cycles and duration in order to assess efficacy and safety against uterine fibroids appropriately, because uterine fibroid is an estrogen-dependent disease.
13)-15)	It is set to ensure that patients with subjective symptoms and objective findings associated with uterine fibroids are included.

4.2 Exclusion criteria

Patients should be confirmed that they do not meet the following exclusion criteria at the time of informed consent, at the start of the screening period, the run-in period, and the treatment period.

4.2.1 Exclusion criteria

1) Patients with a concurrent or past history of hematologic diseases (including thalassemia, sickle cell anaemia, folate deficiency, and coagulopathy) (excluding iron deficiency anaemia and latent iron deficiency anaemia)
2) Patients with a history of severe hypersensitivity or severe allergy to sanitary products
3) Patients with abdominal pain lower due to irritable bowel syndrome or severe cystitis interstitial
4) Patients with concurrent pelvic inflammatory disease or a history of pelvic inflammatory disease within 8 weeks before the start of the screening period
5) Patients with a history of total hysterectomy or bilateral oophorectomy
6) Patients with concomitant thyroid dysfunction accompanied by menstruation irregular or those who are judged by the investigator or subinvestigator to have the possibility of menstruation irregular due to thyroid dysfunction
7) Patients who are judged by the investigator or subinvestigator to have significant metrorrhagia or significant bleeding anovulatory
8) Patients with concurrent abnormal genital haemorrhage that cannot be diagnosed
9) Patients who have used anticoagulants, antiplatelet drugs, tranexamic acid, or selective estrogen-receptor modulators within 4 weeks before the start of the run-in period (excluding topical preparations and dietary supplements)
10) Patients who have used oral contraceptives or sex hormones (norethindrone, norethisterone, medroxyprogesterone, estrogen, or other progestins) within 8 weeks before the start of the run-in period
11) Patients who have received gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists, dienogest, danazol, or aromatase inhibitors within 16 weeks before the start of the run-in period (patients treated with the extended-release formulation follow the exclusion criteria 12) and 13))
12) Patients who received a 4-week extended-release formulation of a GnRH agonist or GnRH antagonist within 20 weeks before the start of the run-in period
13) Patients who have received a long-term sustained release formulation for 12-week or 3-month of a GnRH agonist or GnRH antagonist within 28 weeks before the start of the run-in period
14) Patients who have received drugs that prolong the QT/QTc interval at the start of the screening period
15) Patients with a complication of clinically significant cardiovascular disease (including myocardial infarction and angina unstable that occurred within 24 weeks before the start of the screening period)
16) Patients with a history of risk factors for Torsades de pointes (including heart failure, hypokalemia, and a family history of long QT syndrome)
17) Patients with any of the following in 12-lead ECG at the start of the screening, run-in, or treatment period:

- Abnormal ECG findings of clinical concern
- QTc interval > 470 msec

18) Patients with any of the following measurements of blood pressure at the start of the screening, run-in, or treatment period:
- Systolic blood pressure ≥ 180 mmHg
- Diastolic blood pressure ≥ 110 mmHg

19) Patients with any of the following measurements of clinical laboratory tests at the start of the screening or run-in period:
- Blood hemoglobin concentration < 8 g/dL
- Any of ALT, AST, or total bilirubin, ≥ 2 × ULN
- Serum creatinine of ≥ 2.0 mg/dL

20) Patients with positive* results of cervical cytology performed within 1 year before the start of the screening period (if no test results are available, cervical cytology should be performed to obtain the results by the start of the treatment period)

* "Positive" is defined as cases other than Class I or II in the classification by Japan Association of Obstetricians and Gynecologists or cases other than Negative for intraepithelial lesion of malignancy (NILM) in the Bethesda system classification.

21) Patients with a concurrent or past history of active liver disorder or jaundice
22) Patients with concurrent malignant tumor or with a history of malignant tumor within 5 years before informed consent
23) Patients with a concurrent or past history of any of the following diseases which severity is severe and who are considered unsuitable for the study by the investigator or subinvestigator:
- Renal disorders, cardiovascular diseases, endocrine diseases, metabolic diseases, pulmonary diseases, gastrointestinal diseases, neurological diseases, urological diseases, immune diseases

24) Patients with a concurrent or past history of hypersensitivity (including allergy) to synthetic GnRH, GnRH agonists, or GnRH antagonists
25) Patients with a history of severe drug hypersensitivity (including anaphylactic shock)
26) Patients with a concurrent or past history of drug abuse (defined as illegal use of drugs)
27) Patients with a concurrent or past history of alcoholism
28) Patients with psychiatric diseases (especially depression-like symptoms) or suicide attempts attributable to psychiatric diseases and who are considered unsuitable for the study by the investigator or subinvestigator
29) Patients who are pregnant or breastfeeding, who wish to become pregnant during the study period, or who are not willing to use contraception in an appropriate manner
30) Patients who received another investigational product within 24 weeks before informed consent
31) Patients who have previously received KLH-2109 (including placebo)
32) Patients who failed to screen after re-enrollment
33) Other than the above, patients considered unsuitable for the study by the investigator or subinvestigator

4.2.2 Rationale for exclusion criteria

1)-13), 31), 32)	It is set to evaluate the efficacy of KLH-2109 appropriately.
14)-27), 33)	It is set from the viewpoint of the safety assurance of subjects.
28)	It is set because it may affect compliance with the protocol.
29)	Since the safety of KLH-2109 in pregnant women and infants/fetuses has not been established, these criteria are selected in consideration of safety.
30)	It is set because patients who have received other investigational products are necessary to keep a certain period of time, considering that drug interactions of KLH-2109 with other investigational products and the occurrence of late adverse drug reactions of other investigational products cannot be ruled out and that ethical considerations should be taken.

4.3 Screening failure

Screen failures are defined as subjects who provide informed consent but are not assigned to the investigational product for the treatment period. For screen failures, the date of informed consent, gender, date of birth, race, adverse event, date of discontinuation, and reason for discontinuation will be recorded in the case report form (CRF).

Subjects who fall into screen failures before receiving the investigational product for the run-in period are allowed to be re-enrolled. Informed consent should be separately obtained from re-enrolled subjects according to "5 Informed Consent of Subjects." After re-enrollment, further re-enrollment is not permitted according to the exclusion criterion 32).

4.4 Subject withdrawal criteria

4.4.1 Subject withdrawal criteria

1) Adverse events

- If the investigator or subinvestigator judges that the subject's withdrawal from the study is required due to an adverse event
- If the subject dose not wish to continue participation in the study due to an adverse event
- If liver function test values meet any of the following criteria:
  - ALT or AST > 8 × ULN
  - ALT or AST > 5 × ULN for at least 2 weeks
  - ALT or AST > 3 × ULN and total bilirubin> 2 × ULN
  - ALT or AST > 3 × ULN and INR > 1.5
  - ALT or AST > 3 × ULN and any of the following symptoms:
    - Fatigue
    - Nausea
    - Vomiting
    - Pain or tenderness in the right upper abdomen
    - Pyrexia
    - Rash

- Eosinophilia (>5%)

- If the result of the 12-lead ECG measurement meets any of the following criteria:
  - QTc interval > 500 msec
  - Prolongation of QTc interval by >60 msec from the maximum value before the first dose (at any of the 3 time points: at the start of the screening period, at the start of the run-in period, or at the start of the treatment period before administration of the investigational product for the treatment period)

2) Lack of efficacy (insufficient efficacy)

- If the investigator or subinvestigator judges that there are unacceptable risks to subjects due to lack of efficacy and continuation of the clinical study

3) Subject's voluntary withdrawal from the study (withdrawal due to adverse events is classified as 1) and withdrawal due to lack of efficacy is classified as 2))

4) Significant deviation from the protocol during the study period (from the date of informed consent to the end of the follow-up period)

- If GCP violations are found
- If it is found that subjects do not meet inclusion criteria or meet exclusion criteria of the protocol after administration of the investigational product for the treatment period
- If the investigational product for the treatment period other than the indicated drug number is administered

5) Pregnancy

6) Discontinuation of the entire study

7) Discontinuation of the study at the study site

8) Lost to observation or follow-up

- If loss of contact with subjects makes it impossible to continue the study

9) Blood hemoglobin level decreased to <8 g/dL with or without the use of iron preparation

10) Other than the above, if the investigator or subinvestigator judges that the discontinuation of the study is necessary (the details of the reason should be recorded in the CRF)

4.4.2 Subject removal procedure

- When cases that fall into "4.4.1 Subject withdrawal criteria" occur during the study period, the investigator or subinvestigator promptly should ask the subject to visit the hospital and decide to discontinue the clinical study. The laboratory parameters specified for the test at the time of discontinuation should be measured and evaluated and the date and reason for discontinuation will be recorded in the CRF. If the subject is withdrawn from the study during the treatment period, the follow-up period will start on the day following the test at the time of discontinuation.
- In case of study discontinuation due to adverse events, the investigator or subinvestigator should promptly take appropriate measures and follow-up according to "9.13.10 Follow-up of adverse events and serious adverse events."
- In case of study discontinuation due to falling into the withdrawal criteria related to liver function test values, the investigator or subinvestigator should submit the specified documents to the sponsor within

5 days of the decision to discontinue. If the event is judged to be a serious adverse event, follow "11.2 Measures and handling of serious adverse events."

- If subjects are unable to visit the hospital, the investigator, subinvestigator, or study collaborators should promptly confirm the reason for the inability and subsequent progress. The date of discontinuation is that on which the investigator or subinvestigator judges it to be discontinued.

5. Informed Consent of Subjects

5.1 Time to obtain informed consent

The written informed consent must be obtained by the start of the screening period (before performing the tests specified in this study).

5.2 Procedure for obtaining informed consent

The investigator should prepare a written informed consent form and a consent form by referring to the documents and information provided by the sponsor (including reference examples of written informed consent forms and consent forms), which are necessary to prepare the written informed consent form and obtain the approval of the institutional review board (IRB) in advance.

The investigator or subinvestigator should select subjects who fully consider the objectives of the study from ethical and scientific viewpoints. Subjects who lack the ability to consent will not be included. When selecting a person who is likely to suffer an unreasonable disadvantage due to not participating in the clinical study, sufficient consideration should be given so that the consent of the person is given voluntarily.

Prior to participation in the study, the investigator or subinvestigator should explain the study to the subject using the informed consent form. The investigator or subinvestigator should provide the subject with an opportunity to ask questions. After sufficiently answering the questions and confirming that the subject fully understands the explanation, the investigator or subinvestigator will obtain the subject's voluntary consent to participate in the study in writing (consent form). The consent form should be dated and signed by the investigator or subinvestigator who provided the explanation and dated and signed by the subject. If a study collaborator provides a supplementary explanation, the collaborator should also sign the form with a date.

The investigator or subinvestigator should hand over the copies of the informed consent form and the consent form to the subject and retain the original of the consent form at the study site.

6. Investigational product

6.1 Investigational product

Investigational product	Strength/dosage form
KLH-2109 Tablets 100 mg	A pale yellow film-coated tablet containing 100 mg of KLH-2109 free form in a tablet
KLH-2109 Tablets placebo	A pale yellow film-coated tablet containing 0 mg of KLH-2109 in a tablet KLH-2109 Tablets placebo cannot be distinguished from KLH-2109 Tablets 100 mg.

6.2 Investigational product management

The investigational product manager will appropriately manage and store the investigational products. Details are in accordance with the procedures specified separately.

6.3 Randomization and blinding

6.3.1 Randomization

Eligible subjects of main registration will be randomly assigned by interactive web response system (IWRS) to KLH-2109 200 mg or placebo in a ratio of 1:1.

6.3.2 Blinding

- The allocation manager of investigational products prepares the investigational product allocation table and the emergency key code in accordance with the separately specified SOPs and retains them until unblinding to maintain the blinding of all relevant persons.
- To maintain blinding, pharmacodynamic tests (LH, FSH, E2, and progesterone) will not be measured outside the pharmacodynamic or clinical laboratories during the study period. The results of pharmacodynamic tests will be retained and managed at the pharmacodynamic or clinical laboratories until unblinding. Any information that can identify the treatment group will be reported to the sponsor and the study site after unblinding.
- The results of plasma concentrations of KLH-2109 (unchanged form) and KP017 (major metabolite) will be retained and managed by the laboratory for the drug concentration measurement until unblinding. Any information that can identify the treatment group will be reported to the sponsor and the study site after unblinding.

6.4 Unblinding of emergency key codes

If it is necessary to immediately identify the investigational product in emergency situations, the emergency key code of the drug number should be unblinded according to the following unblinding procedure to identify the drug:

1) In the event of an emergency, the investigator or subinvestigator should promptly take appropriate measures, check the subject's health, and report to the sponsor. If it is deemed necessary to break the emergency key code to ensure the safety of the subject, the investigator or subinvestigator should request the sponsor to break the code.
2) If the investigator or subinvestigator requests to break the emergency key code, and if the sponsor determines that it is necessary to break the emergency key code, the sponsor will open the emergency key code for the drug number and report the result to the investigator.
3) The investigator should prepare a CRF and a “record of breaking the investigational product allocation code ahead of schedule” for the subject with the drug number and submit them to the sponsor.

6.5 Unblinding

The allocation manager of investigational products confirms that blinding is maintained throughout the course of the study and unblinds the investigational product allocation table. Details are in accordance with the procedures specified separately.

7. Study Methods

A placebo-controlled, multicenter, randomized, double-blind, parallel-group comparative study

Study Design

	Screening period	Run-in period	Treatment period 12 weeks	Follow-up period 4 weeks
KLH-2109 group		Placebo Once daily orally	KLH-2109 200 mg Once daily orally	
Placebo group		Placebo Once daily orally	Placebo Once daily orally	

7.1 Overall structure of the clinical study

1) Screening period

After informed consent is obtained, the screening period will be defined as the period from the visit at the start of the screening period (Visit 1) to the day before the start of the run-in period.

Subjects will keep a daily symptom diary from the visit at the start of the screening period.

2) Run-in period

The visit during Days 1 to 5 of the first menstruation after the start of the screening period will be defined as the start of the run-in period (Visit 2). However, if the subject meets the inclusion criteria for the start of the run-in period but cannot visit the hospital during Days 1 to 5 of the first menstruation after the start of the screening period, the visit during Days 1 to 5 of the second menstruation may be defined as the start of the run-in period. The run-in period is defined as the period from the start of the run-in period to the day before the start of the treatment period. After the start of the run-in period, subjects should visit the hospital in the morning whenever possible.

Subjects will keep daily symptom diaries.

3) Treatment period

The visit during Days 1 to 5 of the second menstruation after the start of the screening period will be defined as the start of the treatment period (Visit 3). However, if the subject starts the run-in period during Days 1 to 5 of the second menstruation after the start of the screening period, the visit during Days 1 to 5 of the third menstruation may be defined as the start of the treatment period. A total of 12 weeks from the start of the treatment period is defined as the treatment period. From the visit at the start of the treatment period (Visit 3) to Week 12 (Visit 6) of the treatment period, subjects should visit the hospital in the morning whenever possible.

Subjects will keep daily symptom diaries until the day before the visit at Week 12 of the treatment period (the last day of the administration of the investigational product for the treatment period).

4) Follow-up period

A total of 4 weeks from the end of the treatment period is defined as the follow-up period. If the subject is withdrawn from the study during the treatment period, the follow-up period will be 4 weeks following the test at the time of discontinuation.

7.2 Dosage and administration

7.2.1 Dosage and administration

1) Screening period

The investigational products will not be administered.

2) Run-in period

Two tablets of KLH-2109 placebo will be orally administered once daily (in the morning whenever possible) in a single-blind manner. Administration will be initiated from the visit at the start of the run-in period (Visit 2) until the day before the visit at the start of the treatment period (Visit 3). The investigational drug will be administered at the study site after various tests on the visit at the start of the run-in period.

3) Treatment period

Two tablets of KLH-2109 100 mg or KLH-2109 placebo will be orally administered once daily (in the morning whenever possible) for 12 weeks in a double-blind manner.

Administration will be initiated from the visit at the start of the treatment period (Visit 3) until the day before the visit at Week 12 of the treatment period (Visit 6) The investigational drug will be administered at the study site after various tests except for tests after administration of the investigational drug on the visit at the start of the treatment period. At the visits of Weeks 4 and 8 of the treatment period (Visits 4 and 5), subjects will visit the study site without taking the investigational product for the treatment period, and the investigational product will be administered after various tests.

4) Follow-up period

The investigational products will not be administered.

7.2.2 Rationale for dosage, administration, and duration of administration

The phase I study (Study KLH1101), the Japanese phase II study in patients with endometriosis (Study KLH1202), and the foreign phase III studies in patients with uterine fibroids (Studies Primrose 1 and Primrose 2) have confirmed that KLH-2109 200 mg reduces E2 levels to menopausal level (<20 pg/mL). The foreign phase III studies in patients with uterine fibroids (Studies Primrose 1 and Primrose 2) have investigated the superiority of KLH-2109 200 mg to placebo in the primary endpoint (menstrual blood loss), secondary endpoints (pain symptoms and anaemia), and uterine volume/myoma volume. In the Japanese phase II study in patients with endometriosis (Study KLH1202) and the foreign phase III studies in patients with uterine fibroids (Studies Primrose 1 and Primrose 2), the incidence of adverse drug reactions increased in a dose-dependent manner, but the incidence of adverse drug reactions observed at 200 mg of KLH-2109 were considered to be similar to that observed with existing GnRH agonists and antagonists. Based on these results of clinical studies, 200 mg is selected as the clinical recommended dose for uterine fibroids in Japan.

The PK/PD characteristics of KLH-2109 have been confirmed to be insensitive to food effects. Therefore, the dosage regimen of KLH-2109 is defined as “once daily oral administration” with or without food.

The foreign phase III studies in patients with uterine fibroids (Studies Primrose 1 and Primrose 2) have confirmed that the efficacy of KLH-2109 200 mg for menorrhagia and pain symptoms maximized by Week 12 after administration and maintained through Week 24. The duration of the treatment will be 12 weeks to evaluate the efficacy of KLH-2109 at the time of maximal and stable effect on menorrhagia and pain symptoms.

7.2.3 Rationale for the comparator

By reference to the “Choice of Control Group and Related Issues in Conducting Clinical Studies” (Notification No. 136 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, dated February 27, 2001), placebo is chosen as a comparator to control all potential effects other than the pharmacological action of the investigational drug on actual or apparent disease progression (including natural course of the disease, expectations of subjects or physicians, effects of participating in the clinical study, use of other drugs, and subjective elements of evaluation).

7.3 Concomitant treatment

Overview of concomitant treatment

Concomitant treatment	Category	Screening period	Run-in period	Treatment period	Follow-up period
Concomitant medications	Oral iron preparation	Permitted (If hemoglobin is <10 g/dL at the start of the screening period, an oral iron preparation of 100 mg/day should be used from the start of the run-in period. If an oral iron preparation has been used since before the start of the screening period, the dosage and administration should not be changed. However, the use of an oral iron preparation may be discontinued in case that the investigator or subinvestigator judges that the use is not necessary due to the occurrence of adverse events, etc.)			Permitted (The dosage regimen should not be changed whenever possible.)
	Analgesic drugs	Permitted (It can be used when the subject has severe pain associated with uterine fibroids and needs treatment for adverse events. However, the use to prevent pain associated with uterine fibroids and adverse events is not allowed.)			Permitted (The dosage regimen should not be changed whenever possible.)
	Prohibited concomitant mediations	Prohibited			
	Other concomitant medications	Permitted (The dosage regimen should not be changed whenever possible.)			
Concomitant therapy	Prohibited concomitant therapy	Prohibited			
	Other concomitant therapies	Permitted (The therapies should not be changed whenever possible.)			

7.3.1 Oral iron preparation

If an oral iron preparation is not used at the start of the screening period and hemoglobin is <10 g/dL at the start of the screening period, an oral iron preparation of 100 mg/day should be used from the start of the run-in period to the end of the treatment period (or discontinuation).

If an oral iron preparation has been used since before the start of the screening period, the dosage regimen should not be changed until the end of the treatment period (or discontinuation).

However, the use of an oral iron preparation may be discontinued in case that the investigator or subinvestigator judges that the use is not necessary due to the occurrence of adverse events, etc.

7.3.2 Analgesic drugs

From the start of the screening period to the end of the treatment period (or discontinuation), analgesic drugs may be used if any of the following is applicable:

- When the subject has severe pain associated with uterine fibroids
- When treatment for adverse events is required

When analgesic drugs are used for severe pain associated with uterine fibroids, the drug and dosage regimen should not be changed to the extent possible. The use of analgesic drugs to prevent pain associated with uterine fibroids and adverse events is not allowed.

Analgesic drugs used for treatment of complications since before the start of the screening period should be used without changing the drug and dosage regimen to the extent possible until the end of the follow-up period.

7.3.3 Prohibited concomitant mediations

The use of the following drugs is prohibited from the start of the screening period to the end of the follow-up period.

Category	Names of main drugs
1) GnRH agonist	Buserelin acetate, nafarelin acetate, leuprorelin acetate, goserelin acetate, etc.
2) GnRH antagonist	Cetrorelix acetate, ganirelix, degarelix, relugolix, etc.
3) Hormone drugs mainly composed of LH or estrogen, combination drug of LH and estrogen	Dienogest, Lunabell combination drug, Yaz combination drug, Jemina combination tablet, other hormone drugs (including progesterone, neuroendocrine tumor [NET], norgestrel and chlormadinone acetate), medium-dose pills, low-dose pills, etc.
4) Testosterone derivatives	Danazol, etc.
5) Selective estrogen-receptor modulators (SERMs)	Tamoxifen citrate, raloxifene hydrochloride, bazedoxifene acetate, etc.
6) Aromatase inhibitors	Anastrozole, exemestane, and letrozole, etc.
7) Chinese herbal medicine used to improve menstruation-related symptoms	Shakuyakukanzoto, Keishibukuryogan, Tokishakuyakusan, Tokakujokito, etc.
8) Corticosteroid preparation*	Cortisone, prednisolone, methylprednisolone, triamcinolone, dexamethasone, betamethasone, etc.
9) Anticoagulants, antiplatelets, tranexamic acid	Warfarin, heparin, antithrombin drugs, factor Xa inhibitors, aspirin, ticlopidine, clopidogrel, cilostazol, limaprost, Transamin, tranexamic acid capsules, etc.
10) Anaemia drug	Iron preparation (injection), vitamin B12, vitamin B6, folic acid, etc.
11) Antiepileptics, anticonvulsants, antidepressants, antipsychotics, ergot alkaloids	Phenytoin, sodium valproate, paroxetine, duloxetine, mirtazapine, haloperidol, chlorpromazine, risperidone, olanzapine, ergotamine, methylergometrine, etc.
12) Drugs known to cause QT prolongation*	Quinidine, disopyramide, procainamide, cibenzoline, flecainide, sotalol, nifekalant, amiodarone, bepridil, macrolide antibiotics, new quinolone antibiotics, ST combination drug, itraconazole, hydroxyzine, probucol, haloperidol, chlorpromazine, imipramine, amitriptyline, famotidine, sulpiride, domperidone, doxorubicin, etc.
13) CYP2C8 substrates (limited to drugs that are susceptible to drug interactions and have a narrow therapeutic window)	Repaglinide, paclitaxel, sorafenib, etc.
14) Investigational products other than KLH-2109	Various investigational products

* Excluding topical application

7.3.4 Rationale for the prohibited concomitant mediations

1)-11) They are set to eliminate the effects on the efficacy evaluation of KLH-2109.

12), 13) It is set from the viewpoint of the safety assurance of subjects.

14) It is set considering the safety of subjects because the safety of investigational products currently under development has not yet established and the interaction with KLH-2109 is unknown.

7.3.5 Prohibited concomitant therapy

The use of the following concomitant therapy is prohibited from the start of the screening period to the end of the follow-up period.

- Surgical treatment for uterine fibroids
- Other concomitant therapy that may affect the efficacy evaluation

7.3.6 Rationale for the prohibited concomitant therapies

They are set to eliminate the effects on the efficacy evaluation of KLH-2109.

7.3.7 Other concomitant treatment

Drugs used for treatment of complications at the start of the screening period should be used without changing the dosage regimen to the extent possible until the end of the follow-up period. Concomitant therapy for treatment of complications conducted since before the start of the screening period should not be changed to the extent possible until the end of the follow-up period. No new concomitant medications or therapies should be initiated during the study period. However, concomitant medications and therapies should be initiated in case that the investigator or subinvestigator judges that they are necessary due to the occurrence of adverse events, etc. The dosage regimen of the concomitant drugs and concomitant therapies are allowed to be changed.

7.4 Procedure for enrolling subjects

7.4.1 Tentative registration (at the time of obtaining informed consent)

The investigator or subinvestigator should confirm the eligibility of all subjects who provide informed consent and record the results in the case registration form. The investigator, subinvestigator, or study collaborators should register the results of eligibility in the IWRS during the same day. The IWRS issues the subject identification codes to all enrolled subjects.

7.4.2 Tentative registration (at the start of the screening period)

The investigator or subinvestigator should confirm the eligibility of all subjects for tentative registration (at the time of obtaining informed consent) and record the results in the case registration form. The investigator, subinvestigator, or study collaborators should register the results of eligibility in the IWRS during the same day.

7.4.3 Tentative registration (at the start of the run-in period)

The investigator or subinvestigator should confirm the eligibility of all subjects for tentative registration (at the start of the screening period) and record the results in the case registration form. The investigator, subinvestigator, or study collaborators should register the results of eligibility in the IWRS during the same day.

7.4.4 Main registration

The investigator or subinvestigator should confirm the eligibility of all subjects for tentative

registration (at the start of the run-in period) and record the results in the case registration form. The investigator, subinvestigator, or study collaborators should register the results of eligibility in the IWRS during the same day. The IWRS issues the drug number to all subjects eligible for main registration.

8. Instructions for Subjects

The investigator or subinvestigator should instruct subjects on the following. Instructions as to the efficacy evaluation should be provided in the separately specified procedure.

8.1 Instructions and management on contraception

- Since the safety of KLH-2109 in pregnant women and fetus/infants has not been established, subjects should avoid sexual intercourse as much as possible during the study period and until the first menstruation after the last dose of the KLH-2109.
- Contraception must be used when engaging in sexual intercourse. Effective methods of contraception should be used, such as barrier methods (e.g., condoms) in combination with other methods (e.g., spermicides), or sterilization of the subject or partner. Contraception using basal body temperature method, Ogino method of birth control, or spermicides alone should not be used.
- Prohibited concomitant mediations such as low-dose oral contraceptives and combination drugs of LH and estrogen must not be used.
- If pregnancy is suspected during the study period, subjects should notify the investigator or subinvestigator promptly.

8.2 Instructions and management on study visits and medications

- During the study period, subjects should visit the hospital without taking the investigational product at the same time in the morning as much as possible. Subjects should visit the hospital at least 4 hours after the meal immediately before the visit so that various tests can be performed.
- Subjects must be present at every scheduled visit. At the start of the run-in period and the treatment period, subjects should visit the hospital during Days 1 to 5 of the menstruation. In case of absence due to unavoidable reasons, subjects should contact the hospital in advance.
- On the visit at the start of the treatment period, subjects must not eat any food between the time of administration of the investigational product and the scheduled examination 3 hours after administration of the investigational product.
- During the study period, subjects will take the investigational product at the same time in the morning as much as possible.
- On the day of visit, all investigational products that are left over or forgotten to be taken must be brought to the hospital. If subjects cannot bring the remaining drugs for any reason, the reason should be reported to the investigator, subinvestigator, study collaborators, or investigational product manager.
- If the investigational products are lost, subjects should promptly contact the investigator or subinvestigator to receive the prescription for the missing drugs.
- If administration of the investigational product is discontinued, subjects should visit the hospital

immediately.

- Drugs prescribed other than the investigational product should be taken correctly as indicated.

8.3 Other instruction and management

- Prior to participating in the clinical study, subjects should inform the investigator or subinvestigator of the medications currently in use. When new drugs are prescribed by other departments or medical institutions or when OTC drugs are used, subjects should consult with the investigator or subinvestigator before use. If it is unavoidable to use the drug without consultation, it should be promptly reported to the investigator or subinvestigator.
- When analgesics are used, the type, route of administration, and dose should not be changed as much as possible. Analgesics for prophylaxis are not allowed.
- When visiting another department or medical institution during the study period, subjects should inform the investigator or subinvestigator of the visit in advance and also notify the physician at another department or medical institution of the current participation in the clinical study. In the event that an emergency medical examination is inevitable, subjects should inform the physician at another department or medical institution of the current participation in the clinical study and also promptly report the investigator or subinvestigator about the information including the fact of visiting another medical institution and prescription drug.
- During the period from the start of the screening period to the day before the end of the treatment period (or discontinuation), subjects should use the designated sanitary products provided by the study site. If it becomes difficult to continue using the designated sanitary products due to adverse events or other reasons, subjects will discontinue use of the designated sanitary products and should report to the investigator, subinvestigator, or study collaborators to seek their instructions.
- The symptom diary should be completed daily by subjects themselves. Subjects should inform the investigator, subinvestigator, or study collaborators of any problems with equipment used in the symptom diary.
- If any physical abnormalities are observed at the end of the follow-up period or after the follow-up examinations, subjects will contact promptly the investigator or subinvestigator.
- Any information related to this study, such as materials used in the study, adverse events during the study period, tests performed, and personal impressions of administration of the investigational product, should not be disclosed on the internet (e.g., Facebook, Twitter, and blogs) or on any other media (e.g., newspapers, journals, and advertisements).

9. Investigation, Observation, Examination, and Evaluation Items

9.1 Subject demographic

The following items are investigated and recorded in the CRF:

- Date of obtaining written informed consent
- Year and month of birth
- Gender

- Race
- Height
- Presence or absence of complication at the time of informed consent, disease name if present
- Previous diagnosis of uterine fibroid (time of first diagnosis)
- Type of uterine fibroids (identified at the start of the screening period)
- Previous treatment for uterine fibroid (medications, surgical treatment)
- Birth experience
- Smoking history
- Details on inclusion/exclusion criteria

9.2 Administration of the investigational product

The following items are investigated and recorded in the CRF:

- Drug number
- Start and end dates of administration
- Number of tablets taken
- Whether or not the investigational product for the treatment period was taken (3 and 2 days before the visits* during the treatment period)
- Time of taking the investigational product for the treatment period (the visit at the start of the treatment period and the day before the visits* during the treatment period)
- Conditions of taking the investigational product for the treatment period (the visit at the start of the treatment period and the day before the visits* during the treatment period)

  * Other than the visit at the start of the treatment period (Visit 3)

9.3 Concomitant treatment

9.3.1 Concomitant medications

For all drugs (including over-the-counter drugs) used from the time of informed consent to the end of the follow-up period, details of use (drug name, route of administration, dose*, duration of administration, and reason for administration) will be recorded in the CRF.

* Oral iron preparation only

9.3.2 Concomitant therapy

In case of performing the following concomitant therapies from the time of informed consent to the end of the follow-up period, details of therapies (name of treatment, duration of treatment) will be recorded in the CRF:

- Surgical treatment for uterine fibroids
- Other concomitant therapy that may affect the efficacy evaluation

9.4 Efficacy endpoints

The investigator, subinvestigator, or study collaborators should instruct subjects how to record the symptom diary. The details on the methods for efficacy evaluation should be in accordance with the procedures specified separately.

9.4.1 PBAC score

Subjects will record the presence or absence of bleeding once daily in their symptom diary. If bleeding is observed, the degree of adherence of menstrual blood to the sanitary product, the size and number of blood clots, and the presence or absence of menstrual blood leakage from the sanitary product should be recorded in the symptom diary based on Appendix 1 at each time of changing the sanitary products (napkin or tampon). During the menstruation from the start of the screening period to the day before the end of the treatment period (or discontinuation), subjects will use the sanitary products provided by the sponsor. Other sanitary items may be used to prevent staining of underwear during the period of no bleeding. However, if bleeding is observed, the sanitary items provided by the sponsor should be used immediately.

The investigator or subinvestigator will determine the start date of menstruation at the start of the run-in period and the treatment period by confirming the presence or absence of bleeding based on the symptom diary and the subject's interview. The start date of menstruation is recorded in the CRF. In principle, the same investigator or a subinvestigator will assess the same subject.

9.4.2 NRS score

Subjects will review past 24 hours and self-assess their NRS score for pain symptoms associated with uterine fibroids to record the result once daily in the symptom diary. For the pain associated with uterine fibroids felt most intensely in the day based on Appendix 2, subjects will record an integer from 0 to 10 with a score of 0 for "no pain" and a score of 10 for "maximum possible pain." If analgesics are used, the most severe pain associated with uterine fibroids in the day should be assessed, taking into account the pain experienced before the use of analgesics.

9.4.3 Use of analgesics

Subjects will review past 24 hours and record use or no use of analgesics for severe pain associated with uterine fibroids once daily in the symptom diary.

9.4.4 UFS-QOL

Subjects will review past 4 weeks and assess symptoms of uterine fibroids and QOL associated with health using the questionnaire of Appendix 3. It should be performed prior to other tests and assessments. The date and results of the assessment should be recorded in the CRF.

9.4.5 PGIC

Subjects will assess their general symptoms associated with uterine fibroids compared with those before the start of the run-in period using the questionnaire of Appendix 4. It should be performed prior to other tests and assessments. The date and results of the assessment should be recorded in the CRF.

9.4.6 Myoma volume and uterine volume

The investigator or subinvestigator will measure three major diameters of myomas and the uterus (D1, D2, and D3) by transvaginal ultrasonography. Of the myomas measured by transvaginal ultrasonography at the start of the screening period, the myoma with the longest diameter (D1) will be identified as the largest myoma and the same myoma will be measured during the study period. The date and results of

the measurement should be recorded in the CRF. Images at the time of measurement will be retained at the study site. In principle, the same investigator or a subinvestigator will measure the same subject using the same test devices.

Myoma volume and uterine volume will be calculated by the sponsor using the following formula:

Measurement results:

D1: longest diameter of myoma or uterus (unit: cm)

D2: longest diameter perpendicular to D1 (unit: cm)

D3: longest diameter perpendicular to the plane D1/D2 passing through the intersection point of D1 and D2 (unit: cm)

Calculation formula:

Myoma volume or uterine volume: $D1 \times D2 \times D3 \times \pi/6$ (unit: cm^3)

9.5 12-lead ECG

Prior to blood sampling, the 12-lead ECG measurement should be performed after resting in a supine position (for approximately 5 minutes). The date of measurement (including the time of measurement at the start of the treatment period), physician's assessment (normal, clinically insignificant abnormality, clinically significant abnormality), and ECG parameters (RR interval, PR interval, QRS interval, QT interval, and heart rate) should be recorded in the CRF. If any clinically significant abnormality is assessed, the relevant complication or adverse event should be recorded in the CRF. In principle, the test devices used for the same subject should be the same throughout the study period.

9.6 Vital signs (blood pressure, pulse rate, body temperature)

Systolic blood pressure, diastolic blood pressure, and pulse rate will be measured after rest in a sitting position (for approximately 5 minutes). Body temperature is measured in the axilla. The date and results of the measurement should be recorded in the CRF. In principle, the test devices used for the same subject should be the same throughout the study period.

9.7 Body weight

Body weight is measured. The date and results of the measurement should be recorded in the CRF. In principle, the test devices used for the same subject should be the same throughout the study period.

9.8 Clinical laboratory tests

The following tests will be performed at the time of intensive measurement by the clinical laboratory. CRFs will include whether or not sample collection is performed.

Intensive measurement items by the clinical laboratory

Clinical laboratory tests	Items
Hematology tests	Hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, APTT, INR, PT
Blood biochemistry tests	Ferritin, Na, K, Ca, P, Fe, creatinine, total bilirubin, total protein, albumin, AST, ALT, γ-GTP, ALP, creatine kinase, uric acid, urea nitrogen, LDH, HDL-cholesterol, LDL-cholesterol, total cholesterol, triglyceride
Urinalysis	Protein, sugar, specific gravity, pH, urobilinogen, ketone bodies

9.9 Pregnancy test

A pregnancy test (qualitative urinalysis) will be performed in an in-house laboratory to check for pregnancy. The date of test and presence or absence of pregnancy will be recorded in the CRF.

9.10 Pharmacodynamic tests

9.10.1 E2

E2 will be measured at the time of intensive measurement by the pharmacodynamic laboratory. Details are in accordance with the study plan specified separately. The date and time of blood collection are recorded in the CRF.

9.10.2 LH, FSH, progesterone

LH, FSH, and progesterone will be measured at the time of intensive measurement by the clinical laboratory. The date and time of blood collection are recorded in the CRF.

9.11 Pharmacokinetics

Plasma concentrations of KLH-2109 (unchanged form) and KP017 (major metabolite) will be determined by LC- MS/MS method at the laboratory for the drug concentration measurement. Details are in accordance with the study plan specified separately. The date and time of blood collection are recorded in the CRF.

9.12 Time to menstrual recovery

The investigator or subinvestigator will determine the start date of the first menstrual period after the last dose of the investigational product for the treatment period based on the subjects' interview. The start date of menstruation is recorded in the CRF. If the first menstruation is not observed by the visit at the end of the follow-up period, the subject should be followed up as much as possible by telephone or other means until the first menstruation recovery is observed. If surgery or hormone therapy for uterine fibroids is performed before the first menstruation recovery, the follow-up should be completed and the reason for the completion of the follow-up should be recorded in the CRF.

9.13 Adverse events

9.13.1 Definition of adverse events

An adverse event is any untoward or unexpected sign, symptom, or worsening of complication or disease in a subject and that does not necessarily have to have a causal relationship with the investigational product.

- Examples considered as adverse events
  - Specified or diagnosed signs and symptoms (abnormal test values, abnormal findings, and symptoms associated with the adverse event are not regarded as adverse events)
  - Abnormal test results or abnormal findings requiring treatment
  - Abnormal test results or abnormal findings judged by the investigator or subinvestigator as exceeding the physiological variability of the subject
  - Complications, preexisting symptoms, or existing findings judged by the investigator or

subinvestigator to have worsened (increased in frequency or worsened in severity) beyond the predictable range from before informed consent

– Adverse events that have worsen after administration of the investigational product for the treatment period

- Examples not considered as adverse events
  – A disease or condition that has been confirmed or identified before informed consent is within the predictable range of expected daily variability (including seasonal variation) or has not worsened
  – Surgical procedures such as endoscopic examination, appendectomy, and suture removal after skin suture, or medical procedures
  – Expected worsening of uterine fibroids and symptoms associated with uterine fibroids (worsening beyond the predictable range is regarded as an adverse event)

9.13.2 Definition of serious adverse events

A serious adverse event is defined as the following adverse event. If a serious adverse event occurs, the symptoms or laboratory items, and the reason for judgement as serious will be recorded in the CRF.

1) results in death
2) is life-threatening
3) requires inpatient hospitalisation or prolongation of existing hospitalisation
4) results in persistent or significant disability/incapacity
5) is a congenital anomaly/birth defect
6) Other event or reaction that is judged as a medically significant event or reaction (serious according to 1) to 5))

Other event or reaction that is judged as a medically significant event or reaction (serious according to 1) to 5)) is defined as a medical event that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject , or may require intervention or treatments to prevent one of the outcomes defined as 1) to 5).

9.13.3 Duration of collection of adverse events and serious adverse events

Adverse events and serious adverse events will be collected from the time of obtaining informed consent to the end of the follow-up period.

9.13.4 Methods for investigating adverse events

The investigator or subinvestigator will take care not to affect voluntary reports from subjects, when interviewing subjects. General questions such as “How have you been since your last visit?” will be asked.

9.13.5 Record of adverse events

The investigator or subinvestigator should record the name of the adverse event, date of onset, date of resolution, severity, seriousness, action taken with the investigational product, other action taken, outcome, and causal relationship to the investigational product in the CRF.

The name and seriousness of the adverse event occurring from the informed consent to before

administration of the investigational product for the treatment period should be recorded in the CRF.

9.13.6 Severity of adverse events

The severity of adverse events is defined as follows:

- Mild: Does not limit activities of daily living or slightly limit activities of daily living but does not require treatment or requires simple treatment
- Moderate: Limits activities of daily living and requires treatment
- Severe: Results in inability to perform activities of daily living or needs systemic treatment

9.13.7 Actions taken with the investigational product

Actions taken with the investigational product are defined below:

- Discontinuation: When the investigational product is discontinued due to the adverse event, including the subject's request
- Treatment interruption: When the administration of the investigational product is interrupted due to the adverse event, including the subject's request
- No change in dose: When the administration of the investigational product is continued without any action taken with the investigational product
- Unknown: When action taken with the investigational product cannot be confirmed
- Not applicable: When the administration of the investigational product is completed or discontinued before the onset of the adverse event

9.13.8 Outcome of adverse events

Outcomes of adverse events are defined below:

- Resolved: Elimination or recovery of symptoms, and return of laboratory values to within the reference range or to levels similar to those before treatment
- Improved: Reduced severity of symptoms/abnormalities or a trend toward improvement
- Not resolved: Little change in symptoms or abnormal values, or aggravation observed
- Resolved with sequelae: Functional impairment observed that limits daily activities, which is attributed to symptoms or abnormal values
- Death: Death related to symptoms or abnormal values (not applicable to deaths unrelated to symptoms or abnormal values)
- Unknown: Lost to follow up outcome

9.13.9 Causal relationship between adverse events and the investigational product

The investigator or subinvestigator will determine the causal relationship with the investigational product based on conditions of subjects, complications, medical history, concomitant medications, and time-to-onset relationship. Of adverse events occurring after the start of administration of the investigational product for the treatment period, events judged as “related” will be regarded as adverse drug reactions.

The causal relationship between adverse events that occur secondary to adverse events and the investigational product will be determined independently.

- Case related to the investigational product
  - If it disappears after discontinuation of administration
  - If it recurs after resumption of administration
  - If the causal relationship with the investigational product or similar drugs has been established
  - If there are no confounding risk factors
  - If there is consistency with the exposure dose and duration
  - If involvement of the investigational product can almost be explained based on accurate medical history
  - If there is no reasonable possibility that the concomitant treatment is attributable
- Case not related to the investigational product
  - If another cause is the most reasonable factor for the occurrence of the adverse event
  - If it is considered unlikely that there is a causal relationship between the investigational product and the adverse event based on the timing of onset of the adverse event
  - If the occurrence of the adverse event is considered incidental (e.g., the same event was frequently observed prior to the study and the adverse event during the study falls within that range)

9.13.10 Follow-up of adverse events and serious adverse events

Among the serious adverse events that occurs from the time of informed consent to the administration of the investigational product for the treatment period and all adverse events that occurs after the start of administration of the investigational product for the treatment period, those for which the investigator or subinvestigator judges that the symptoms (including laboratory values) have not recovered or disappeared to the pre-event state by the end of the follow-up period will be followed up.

The follow-up will be closed if any of the follow applies:

- If the investigator or subinvestigator judges that the event resolves or disappears
- If the investigator or subinvestigator judges that further follow-up is not necessary

Among subjects who withdraw from the study due to adverse events, if they discontinue due to meeting the withdrawal criteria related to liver function test values or 12-lead ECG, they will be followed up according to the following:

- In case of discontinuation due to falling into the withdrawal criteria related to liver function test values, subjects should be followed up until the abnormal values of the liver function test return to within the reference range or to levels comparable to those on the first day of administration of the investigational product for the treatment period.
- In case of discontinuation due to falling into the withdrawal criteria related to 12-lead ECG, subjects should be followed up until the following time points:
  - In case of discontinuation because the QTc interval exceeds 500 msec, the follow-up should be performed until it returns to <480 msec.
  - In case of discontinuation because the QTc interval is prolonged by >60 msec from the maximum before the first dose, the follow-up should be performed until it returns to by <30 msec.

10. Investigation, Observation, Examination, and Evaluation Items per Time to Conduct

10.1 At the start of the screening period (Visit 1)

- Written informed consent
- Confirmation of subject demographic
- Confirmation of adverse events, concomitant medications and therapies
- 12-lead ECG
- Vital signs (blood pressure, pulse rate, body temperature)
- Body weight
- Laboratory tests (hematology, blood biochemistry, urinalysis)
- Pregnancy test
- Myoma volume and uterine volume*

  * Only when transvaginal ultrasonography is performed before informed consent and informed consent is obtained and the screening period starts on the same day, the result of transvaginal ultrasonography may be used as data at the start of the screening period.
- Confirmation of eligibility and registration
- Guidance on symptom diaries

10.2 At the start of the run-in period (Visit 2)

- Confirmation of subject demographic
- Checking symptom diaries
- Confirmation of the start date of menstruation
- Confirmation of adverse events, concomitant medications and therapies
- 12-lead ECG
- Vital signs (blood pressure, pulse rate, body temperature)
- Body weight
- Laboratory tests (hematology, blood biochemistry, urinalysis)
- Pregnancy test
- Confirmation of eligibility and registration
- Prescription of the investigational product for the run-in period

10.3 At the start of the treatment period (Visit 3)

- Confirmation of subject demographic
- Checking symptom diaries
- Confirmation of the start date of menstruation
- Confirmation of compliance
- UFS-QOL
- Confirmation of adverse events, concomitant medications and therapies
- 12-lead ECG (before administration of the investigational product for the treatment period)
- Vital signs (blood pressure, pulse rate, body temperature)

- Body weight
- Laboratory tests (hematology, blood biochemistry, urinalysis)
- Pregnancy test
- Pharmacodynamic tests
- Myoma volume and uterine volume
- Confirmation of eligibility and registration
- Prescription and administration of the investigational product for the treatment period
- 12-lead ECG (3 hours after administration of the investigational product for the treatment period [acceptable range ± 30 minutes])
- Pharmacokinetics (3 hours after administration of the investigational product for the treatment period [acceptable range ± 30 minutes])

10.4 At Week 4 of the treatment period (Visit 4)

- Checking symptom diaries
- Confirmation of compliance
- Confirmation of adverse events, concomitant medications and therapies
- 12-lead ECG (before administration of the investigational product for the treatment period)
- Vital signs (blood pressure, pulse rate, body temperature)
- Body weight
- Laboratory tests (hematology, blood biochemistry, urinalysis)
- Pregnancy test
- Pharmacodynamic tests
- Pharmacokinetics (before administration of the investigational product for the treatment period)
- Myoma volume and uterine volume
- Prescription of the investigational product for the treatment period

10.5 At Week 8 of the treatment period (Visit 5)

- Checking symptom diaries
- Confirmation of compliance
- Confirmation of adverse events, concomitant medications and therapies
- 12-lead ECG (before administration of the investigational product for the treatment period)
- Vital signs (blood pressure, pulse rate, body temperature)
- Body weight
- Laboratory tests (hematology, blood biochemistry, urinalysis)
- Pregnancy test
- Pharmacodynamic tests
- Pharmacokinetics (before administration of the investigational product for the treatment period)
- Myoma volume and uterine volume
- Prescription of the investigational product for the treatment period

10.6 At Week 12 of the treatment period or discontinuation of the treatment period (Visit 6)

- Checking symptom diaries
- Confirmation of compliance
- UFS-QOL
- PGIC
- Confirmation of adverse events, concomitant medications and therapies
- 12-lead ECG
- Vital signs (blood pressure, pulse rate, body temperature)
- Body weight
- Laboratory tests (hematology, blood biochemistry, urinalysis)
- Pregnancy test
- Pharmacodynamic tests
- Pharmacokinetics
- Myoma volume and uterine volume

10.7 At Week 4 of the follow-up period (Visit 7)

- Confirmation of adverse events, concomitant medications and therapies
- Confirmation of menstrual recovery
- 12-lead ECG
- Vital signs (blood pressure, pulse rate, body temperature)
- Body weight
- Laboratory tests (hematology, blood biochemistry, urinalysis)
- Pregnancy test
- Pharmacodynamic tests

11. Items to Ensure Safety of the Clinical Study

11.1 Measures to be taken in case of adverse events

If an adverse event occurs during the study period, the investigator or subinvestigator should take appropriate measures to ensure the safety of the subject. If the event is applicable to "9.13.10 Follow-up of adverse events and serious adverse events," the follow-up should be conducted in accordance with the section.

11.2 Measures and handling of serious adverse events

11.2.1 Measures to serious adverse events

If a serious adverse event listed in "9.13.2 Definition of serious adverse events" occurs, the investigator or subinvestigator should take appropriate emergency measures to ensure the subject's recovery.

11.2.2 Handling of serious adverse events

The investigator or subinvestigator should contact the sponsor within 24 hours following learning of a serious adverse event. The investigator will submit the prescribed documents to the sponsor within 3 days and promptly report to the head of the study site in accordance with the procedure of the study site.

11.3 Measures and handling to pregnancy

If pregnancy is confirmed or suspected in a female subject during the study period, the investigator or subinvestigator should immediately discontinue the administration of the investigational product to the subject. If the investigator or subinvestigator becomes aware of any information that suggests pregnancy, the investigator or subinvestigator should promptly notify the sponsor of the information. In addition, the investigator or subinvestigator will follow up the progress of pregnancy up to delivery and the offspring up to approximately one and a half years of age and inform the sponsor of any information obtained. However, the follow up will be not required if the subject is in the placebo group as a result of unblinding.

11.4 Collection and provision of safety information

11.4.1 Collection of new safety information

The sponsor should continue to collect and evaluate information that could adversely affect the safety of subjects, affect the conduct of the study, or change the IRB's approval of the continuation of the study.

11.4.2 Provision of new safety information

The sponsor should promptly notify in writing all investigators involved in the study, the heads of the study sites, and the IRB through the heads of the study sites, of any new information that may adversely affect the safety of subjects or the conduct of the study. If the sponsor, relevant committees including the IRB, and the head of the study site have agreed in advance, the sponsor can simultaneously inform the committees of only the notifications relating to Article 20, Paragraphs 2 and 3 of the GCP.

If it is deemed that the information may affect the subjects' willingness to continue the study, the investigator or subinvestigator will immediately communicate the information to subjects and confirm the subjects' willingness to continue the study. At that time, the fact that the information has been communicated to subjects and the results of confirmation of subjects' willingness to continue the study should be recorded in a document (e.g., medical record). If it is deemed necessary to revise the informed consent form, the investigator should promptly revise the informed consent form based on the information and obtain approval of the IRB in advance. The investigator or subinvestigator should re-explain the information using the revised informed consent form and obtain subjects’ free will consent to continue participation in the study. In principle, no new subject will be enrolled in the study until the revised informed consent form is approved. However, if the sponsor and the investigator judge that there is no need to change, discontinue, and interrupt the study, new subjects may be enrolled. In this case, the original informed consent form should be used and any new safety information that may affect the subjects' willingness to continue in the study should be communicated and recorded. Re-consent should be obtained using the revised informed consent form after approval by the IRB.

12. Discontinuation of the Clinical Study

12.1 Discontinuation of the clinical study by the sponsor

1) When the clinical study is interrupted or discontinued, the sponsor should promptly notify in writing the heads of all the study sites involved the clinical study of the details and the reasons.
2) If the head of the study site is notified that the sponsor decides to interrupt or discontinue the study, the head of the study site should promptly inform the investigator and relevant committees including the IRB in writing and provide a detailed written explanation of the interruption or discontinuation.
3) If the investigator is notified of the interruption or discontinuation of the study by the head of the study site, the investigator should immediately communicate the decision to subjects and take necessary measures.

12.2 Discontinuation of the study by the study site

1) When the investigator interrupts or discontinues the study at his/her own discretion for any of the following and other reasons, the investigator should promptly inform the decision to the head of the study site and report the reason in writing:

- When either the study site or the investigator commits serious violation of the GCP, protocol, or agreements, which may hamper the proper continuation of the study
- When it is difficult to continue the study due to changes in the implementation structure of the study (e.g., personnel change of the investigator)

2) If the head of the study site is notified that the investigator decides to interrupt or discontinue the study, the head of the study site should promptly inform relevant committees including the IRB and the sponsor in writing and provide a detailed written explanation of the interruption or discontinuation.

13. Statistical Analysis

The main analysis methods are shown below. Details are specified in the statistical analysis plan prepared separately before obtaining the informed consent from the first subject.

- Handling of subjects and data will be determined prior to database lock.
- The two-sided significance level of 5% will be used for the statistical test. However, the two-sided significance level of 15% will be used for the analysis of imbalance between groups in subject demographic. Summary statistics will be presented as the number of subjects, mean, standard deviation, minimum, median, maximum, and quartiles.
- Unless otherwise specified, tabulation will be performed by group and by analysis visit.
- For the PBAC score, NRS score, and use of analgesics, baseline will be defined as the period of one menstrual cycle immediately before the start of the treatment period. For other endpoints, baseline will be defined as at the start of the treatment period.

13.1 Analysis set

When the Full Analysis Set (FAS) and the Per Protocol Set (PPS) are used as the analysis set, the analysis will be performed based on the assigned treatment. When the Pharmacokinetic Analysis Set (PKS) and Safety Set (SS) are used as the analysis set, the analysis will be performed based on the

treatment actually received.

1) FAS

Population of subjects who are randomized and receive at least one dose of the investigational product for the treatment period

2) PPS

Population excluded the following subjects from FAS:

- Subjects who do not meet the inclusion criteria
- Subjects who fall into the exclusion criteria related to efficacy evaluation
- Subjects who withdraw from the study during the treatment period
- Subjects with a compliance rate of <75% for the investigational product in the treatment period
- Subjects who have an input rate of <75% for PBAC (bleeding or not) or NRS scores into the symptom diary during the treatment period
- Subjects who receive prohibited concomitant medications or prohibited concomitant therapy before the end of the treatment period

3) PKS

Population of subjects who receive at least one dose of KLH-2109 and have plasma concentration data at least one time point

4) SS

Population of subjects who receive at least one dose of the investigational product for the treatment period

13.2 Analysis Groups

The analysis sets and subjects for the analysis groups are shown in the following table.

Analysis set and subjects

Analysis groups	Analysis sets	Subjects
KLH-2109 200 mg group	FAS, PPS	Subjects who are assigned to KLH-2109 200 mg
	PKS, SS	Subjects who receive KLH-2109 200 mg
Placebo group	FAS, PPS	Subjects who are assigned to placebo
	SS	Subjects who receive placebo

13.3 Disposition of subjects

For eachanalysis set, the presence/absence of discontinuation, and completion or not completion of the follow-up period, the number and proportion of subjects will be presented. Differences between groups will also be examined.

13.4 Demographic and other baseline characteristics

For main subject demographics, summary statistics or the number and proportion of subjects will be presented for overall population and each group, according to the characteristics of the data.

13.5 Efficacy

The FAS will be used for the primary analysis set. As a supplemental analysis, the primary endpoint will be analyzed in the PPS to confirm robustness of the results. If “no bleeding” is entered in the PBAC score (bleeding or not) in the symptom diary, the PBAC score will be handled as 0.

13.5.1 Primary endpoint

- Proportion of subjects with a total PBAC score of <10 from Week 6 to Week 12 after administration of the investigational product
- Proportion of subjects with the maximum NRS score for pain symptoms of ≤1 for 28 days prior to the end of the investigational product administration

13.5.2 Analysis method for primary endpoint

- The number and proportion of subjects with a total PBAC score of <10 from Week 6 to Week 12 after administration of the investigational product and its two-sided 95% CIs (Clopper–Pearson) will be presented for each treatment group. The point estimate of the difference between the KLH-2109 200 mg group and the placebo group (KLH 2109 200 mg group − placebo group) with its two-sided 95% CI (Chan and Zhang) will be presented. Fisher's exact test will be used to confirm the superiority of the KLH-2109 200 mg group to the placebo group.
- The number and proportion of subjects with the maximum NRS score for pain symptoms of ≤1 for 28 days prior to the end of the investigational product administration per group and its two-sided 95% CI will be presented. The point estimate of the difference between the KLH-2109 200 mg group and the placebo group (KLH 2109 200 mg group − placebo group) with its two-sided 95% CI will be presented. Fisher's exact test will be used to confirm the superiority of the KLH-2109 200 mg group to the placebo group.

13.5.3 Analysis method for the secondary endpoints

- Proportions of subjects with a total PBAC score of <10, amenorrhoea (total PBAC score of 0), the maximum NRS score of ≤1, and the maximum NRS score of 0
  - Number and proportion of subjects and its two-sided 95% CIs will be presented.
  - The point estimate of the difference between the KLH-2109 200 mg group and the placebo group with its two-sided 95% CI will be presented.
- Time to a total PBAC score of <10 or amenorrhoea (total PBAC score of 0)
  - The analysis duration will be calculated by the following formula and the Kaplan–Meier estimate will be performed:

    Calculation formula: (Time to a total PBAC score <10 or amenorrhoea) = (The first day for which the total PBAC score <10 or amenorrhoea for all subsequent 42-day periods up to the last day of study treatment was achieved by calculating total PBAC score every 42 days from the first day of study treatment to the last day of study treatment) − (First day of study treatment) + 1
  - Kaplan–Meier plots with overlapped each group will be displayed.
  - The log-rank test will be used to compare the KLH-2109 200 mg group and the placebo group.
- Mean NRS score, proportion of days without symptoms (NRS score for pain symptoms of 0), proportion of days using analgesics, UFS-QOL score
  - Summary statistics of observed values and changes from baseline will be presented.
  - The point estimate of the difference between the KLH-2109 200 mg group and the placebo group with its two-sided 95% CI will be presented.

- Blood hemoglobin, blood hematocrit, serum iron, and serum ferritin
  - Summary statistics of observed values and changes from baseline will be presented.
  - For blood hemoglobin, the point estimate of the difference between the KLH-2109 200 mg group and the placebo group with its two-sided 95% CI will be presented.
- Myoma volume and uterine volume
  - Summary statistics of observed values and percent change from baseline will be presented.
  - The point estimate of the difference between the KLH-2109 200 mg group and the placebo group with its two-sided 95% CI will be presented.
- PGIC
  - The number and proportion of subjects with general symptoms will be presented.
  - The Wilcoxon two-sample test will be used to compare the KLH-2109 200 mg group and the placebo group.

13.6 Safety

The SS will be used for the analysis set and the following analyses will be performed.

- Adverse events and adverse drug reactions
  - Events occurring from the start of administration of the investigational product for the treatment period to the end of the follow-up period will be tabulated.
  - The number of events, the number of subjects with events, incidence and its two-sided 95% CIs will be presented.
  - Fisher's exact test will be used to compare the KLH-2109 200 mg group and the placebo group, and the between-group difference of incidence and its two-sided 95% CI will be presented.
  - The number of events, the number of subjects with events and incidence will be presented as for all events, events leading to death, serious adverse events excluding death, and events leading to discontinuation.
  - The number of subjects with events and incidence will be presented by the total, primary SOC, and PT.
  - The number of events by the total, primary SOC, and PT will be presented by severity.
  - The number of subjects with events and incidence by the total, primary SOC, and PT will be presented by time of onset.
- Laboratory tests (hematology, blood biochemistry, urinalysis)
  - For quantitative values, summary statistics of observed values and changes from baseline, scatter plots before and after administration, and shift tables before and after administration will be presented.
  - For qualitative values, the number and proportion of subjects and shift tables before and after administration will be presented.
- Vital signs and body weight
  - Summary statistics of observed values and changes from baseline, and scatter plots before and after administration will be presented.

- 12-lead ECG
  - For ECG parameters (RR interval, PR interval, QRS interval, QT interval, QTcF interval and heart rate), summary statistics of observed values and changes from baseline will be presented.
  - For QT interval and QTcF interval, baseline and maximum values after administration of the investigational product will be classified into ≤450, >450 to ≤480, >480 to ≤500, and >500 (unit: msec) for each subject. Cross-tabulation of baseline and the maximum values after administration of the investigational product will be performed to show the number of subjects.
  - The maximum change from baseline (maximum prolongation time) will be determined for each subject and the number of subjects will be presented for each evaluation category of ≤30, >30 to ≤60, and >60 (unit: msec).
- Duration from last dose of the investigational product to menstrual recovery
  - Summary statistics will be presented.

13.7 Pharmacokinetics

The PKS will be used for the analysis set. Summary statistics, geometric means, and geometric coefficient of variation of plasma concentrations of KLH-2109 (unchanged drug) and KP017 (major metabolite) will be presented.

13.8 Pharmacodynamic effects

The FAS will be used for the analysis set. Summary statistics of observed values and change from baseline of E2, LH, FSH, and progesterone will be presented.

13.9 Sample size

A total of 78 subjects (39 per group) will be included in the study.

The sample size for the primary endpoint related to menorrhagia, "the proportion of subjects with a total PBAC score of <10 from Week 6 to Week 12 after administration of the investigational product," is calculated based on the results of clinical studies of relugolix, an existing medication for uterine fibroids. KLH-2109 200 mg has been shown to lower serum estradiol levels to menopausal levels (<20 pg/mL), similar to relugolix 40 mg, an existing medication for uterine fibroids. Based on the results of foreign phase III studies (Studies Primrose 1, Primrose 2, LIBERTY 1, and LIBERTY 2) of KLH-2109 and relugolix in uterine fibroid patients with menorrhagia, the efficacy of KLH 200 mg and relugolix 40 mg for menorrhagia is assumed to be comparable. In the Japanese phase II study of relugolix (Study CCT-001), the proportion of subjects with a total PBAC score of <10 from Week 6 to Week 12 after administration of the investigational product (number of subjects) [two-sided 95% CI] was 0.0% (0 of 57 subjects) [0.0, 6.3] in the placebo group and 83.3% (45 of 54 subjects) [70.7, 92.1] in the relugolix 40 mg group.

The sample size required to confirm superiority of KLH-2109 200 mg to placebo is calculated by setting the primary endpoint related to menorrhagia of "the proportion of subjects with a total PBAC score of <10 from Week 6 to Week 12 after administration of the investigational product" as 5% and 83% for placebo and KLH-2109 200 mg, respectively, the two-sided significance level as 5%, and the power

as 90%. The sample size required to confirm superiority of KLH-2109 200 mg to placebo using Fisher's exact test is calculated to be 10 per group.

For the primary endpoint of pain symptoms, "Proportion of subjects with the maximum NRS score for pain symptoms of ≤1 for 28 days prior to the end of the investigational product administration," the sample size is calculated by reference to the results of clinical studies outside Japan. In the pooled analysis of Studies Primrose 1 and Primrose 2, the proportions (numbers) [two-sided 95% CI] of subjects with the maximum NRS score for pain of ≤1 at Week 12 among subjects with menstrual blood loss of ≥100 mL and the maximum NRS score of ≥4 at baseline are 8.8% (10 of 114 subjects) [3.6, 14.0] and 44.0% (55 of 125 subjects) [35.3, 52.7] in the placebo and KLH-2109 200 mg groups, respectively.

The sample size required to confirm superiority of KLH-2109 200 mg to placebo is calculated by setting the primary endpoint related to pain symptoms of "the proportion of subjects with the maximum NRS score for pain symptoms of ≤1 for 28 days prior to the end of the investigational product administration" as 10% and 44% for placebo and KLH-2109 200 mg, respectively, the two-sided significance level as 5%, and the power as 90%. The sample size required to confirm superiority of KLH-2109 200 mg to placebo using Fisher's exact test is calculated to be 39 per group.

A total of 39 subjects per group will be included in the study, based on the sample size required for these 2 primary endpoints.

14. Compliance with the Protocol

14.1 Agreement with the protocol

The investigator shall sign and date the protocol or an alternative document to show that he/she agrees to the contents of the protocol and comply with the protocol.

14.2 Protocol deviations

The investigator and persons involved shall conduct the clinical study in compliance with the protocol previously approved by the IRB. The investigator or subinvestigator will record any deviations from the protocol.

The investigator shall record any failure to comply with the protocol in order to avoid immediate danger to the subject or for other medically compelling reasons. The investigator will immediately submit the document stating such failure and the reason to the sponsor, the head of the study site, and the IRB via the head of the study site to obtain their approval. The investigator will also obtain the approval of the head of the study site and the written agreement of the sponsor via the head of the study site.

15. Ethics

15.1 Compliance with GCP

Under the ethical spirit based on the latest Declaration of Helsinki, this clinical study will be conducted in compliance with Article 14, Paragraph 3 and Article 80, Paragraph 2 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics, and the standards for clinical studies of

pharmaceuticals specified by the Minister of Health, Labour and Welfare(MHLW) in these articles, as well as the "Guideline for Good Clinical Practice" established as the standards specified by MHLW ordinance and the protocol.

15.2 Items related to confidentiality of subjects

In accordance with Article 80, Paragraph 2-10, Paragraph 10 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics, the sponsor shall not divulge any confidential information of subjects obtained during monitoring or auditing.

The head of the study sites shall take necessary measures to ensure the protection of the confidentiality of subjects.

The investigator assures that the subject identification code is used in place of name and identifiable numbers or address, when reporting adverse events and other study-related data.

15.3 Compensation to subjects

- If any health damage attributable to the clinical study occurs to subjects, the study site will take necessary measures including treatment.
- If subjects request or may request the study site to bear compensation or legal liability for health damage due to this study, the study site should immediately contact the sponsor and work together to resolve the problem.
- The sponsor will provide compensation to subjects in accordance with the sponsor's compensation rules if subjects suffer health damage caused by the study.
- In case of being later required to bear legal liability regarding the subject's health damage due to the study, the person responsible will pay the compensation at the responsibility and burden.
- The sponsor will obtain insurance coverage for such compensation or legal liability.

16. Management of Clinical Study

16.1 Quality control and quality assurance of clinical study

The sponsor performs quality control and quality assurance in accordance with the standard operating procedures. The auditor of the sponsor will assess whether or not the clinical study is being conducted in compliance with GCP, the protocol and procedures, independently from the routine monitoring and quality control activities of the study.

16.2 Direct access to source documents

- The term "source document" refers to documents, data, and records that form the basis of factual information about the clinical study or the CRFs. The term "source data" refers to any information recorded in the original record and its assured copy of clinical findings, observations, and other activities in a clinical study that is necessary for the reproduction and evaluation of the clinical study's factual course. The source data shall meet the requirements of attribution, legibility, simultaneity, originality, accuracy, and completeness. When the source data is changed, it should be ensured that the

process can be traced back and the prechange description is not obscured.

- The head of the study site and the investigator should accept monitoring and audits by the sponsor and inspections by the IRB and by the regulatory authority in Japan and overseas and make the source documents available for direct access.
- The sponsor should cross-reference the contents of the CRFs prepared by the investigator with the source documents and other study-related records to ensure their accuracy. The CRFs should be consistent with the source documents.

16.3 Data handling

- The investigator or subinvestigator will record the data collected in this study on the electronic CRFs for all subjects who provide informed consent. The investigator should ensure that all eCRFs are completed correctly and sign the eCRFs. The study site will retain copies of all eCRFs.
- Data on symptom diaries recorded by subjects will be collected using an electronic diary system.
- Laboratory, pharmacodynamic, and pharmacokinetic data will be electronically provided to the sponsor from the external laboratory.

16.4 Retention of records

16.4.1 Study site

The head of the study site shall retain the study-related documents or records until the sponsor notifies that it is no longer necessary to retain them. The head of the study site or the person responsible for the retention of records will take measures to ensure that these records are not lost or destroyed during the retention period and that they can be presented upon request.

The investigator will keep the documents related to the conduct of the clinical study as instructed by the head of the study site.

16.4.2 Institutional Review Board

The organizer of the IRB shall retain the study-related documents or records until the sponsor notifies that it is no longer necessary to retain them. These records should be made available to the regulatory authority upon request.

16.4.3 Notification from the sponsor

The sponsor will notify the head of the study site and the organizer of the IRB via the head of the study site if it is no longer necessary to retain documents or records related to the clinical study that should be retained by the head of the study site or the organizer of the IRB.

16.5 Publication arrangements

The sponsor has a right to possession of the information including unpublished data in this protocol. The information cannot be disclosed to any third party without the written consent of the sponsor. When part or all of the results of this clinical study are to be presented to outside parties such as academic conferences or journals, approval by the sponsor is required in advance.

17. Implementation Structure of the Clinical Study

This clinical study will be designed and conducted by the organization described in the separate volume. The separate volume will be revised independently from this protocol.

18. Revision History of Protocol

Prepared on May 13, 2022 Version: 1.0

Prepared on July 15, 2022 Version: 2.0

19. References

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2) Vilos GA, Allaire C, Laberge PY, et al. The Management of Uterine Leiomyomas. J Obstet Gynaecol Can. 2015;37:157-78.

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4) Mikio Momoeda. Comprehensive gynecologic endocrinology: from basic to clinic. Tokyo: SHINDAN TO CHIRYO SHA, Inc. 2016, p.198-201.

5) ASKA Pharmaceutical Co., Ltd. Package Insert of Relumina® Tablets 40 mg. Revised in December 2021 (1st version, change of indication).

6) Takeda Pharmaceutical Company Limited. Package Insert of Leuplin® for injection. Revised in July 2018 (23rd version).

7) Sanofi K.K. Package Insert of Suprecur® nasal solution 0.15%. Revised in June 2015 (16th version).

8) Kissei Pharmaceutical Co., Ltd. Package Insert of Zoladex® 1.8 mg depot. Revised in January 2017 (13rd version).

9) AbbVie Inc. ORILISSA Prescribing information. February 2021.

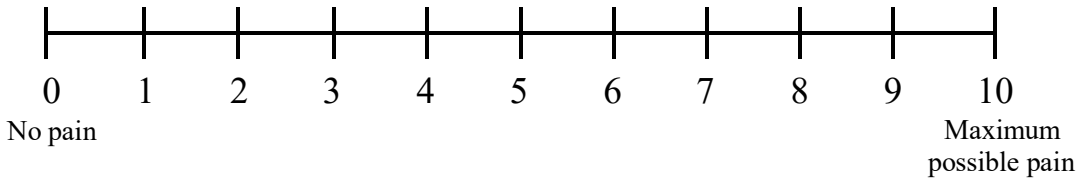
10) Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynaecol. 1990;97(8):734-9.

20. Appendix

Appendix 1 Evaluation of menstrual blood loss

Amount of menstrual blood absorbed by the napkin	Small: 1 point, Medium: 5 points, Large: 20 points
Amount of menstrual blood absorbed by the tampon	Small: 1 point, Medium: 5 points, Large: 10 points
Blood clot	Small (2 cm) : 1 point, Large (3 cm) : 5 points
Leakage of menstrual blood from the napkin or tampon	5 points

Appendix 2 NRS (Numerical Rating Scale)



Appendix 3 UFS-QOL (Uterine Fibroid Symptom and Quality of Life)

Uterine Fibroid Symptom and Health-Related Quality of Life (QOL) Questionnaire (UFS-QOL)

Listed below are symptoms experienced by women who have uterine fibroids. Please consider each symptom as it relates to your uterine fibroids or menstrual cycle. Each question asks how much distress you have experienced from each symptom during the previous 4 weeks[1].

There are no right or wrong answers. Please be sure to answer every question by checking (✓) the most appropriate box.
If a question does not apply to you, please mark (✓) "not at all" as a response.

During the previous 4 weeks[1], how distressed were you by...	Not at all	A little bit	Some-what	A great deal	A very great deal
1. Heavy bleeding during your menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Passing blood clots during menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. Fluctuation in the duration of your menstrual period compared to your previous cycles	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Fluctuation in the length of your monthly cycle compared to your previous cycles	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. Feeling tightness or pressure in your pelvic area	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Frequent urination during the daytime hours	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Frequent nighttime urination	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. Feeling fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

The following questions ask about your feelings and experiences regarding the impact of uterine fibroid symptoms on your life. Please consider each question as it relates to your experiences with uterine fibroids during the previous 4 weeks[1].

There are no right or wrong answers. Please be sure to answer every question by checking (✓) the most appropriate box. If the question does not apply to you, please check "none of the time" as your option.

During the previous 4 weeks[1], how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
9. Made you feel anxious about the unpredictable onset or duration of your periods?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
10. Made you anxious about traveling?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
11. Interfered with your physical activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
12. Caused you to feel tired or worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
13. Made you decrease the amount of time you spent on exercise or other physical activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. Made you feel as if you are not in control of your life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. Made you concerned about soiling underclothes?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
16. Made you feel less productive?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
17. Caused you to feel drowsy or sleepy during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18. Made you feel self-conscious of weight gain?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19. Made you feel that it was difficult to carry out your usual activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20. Interfered with your social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
21. Made you feel conscious about the size and appearance of your stomach?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
22. Made you concerned about soiling bed linen?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

During the previous 4 weeks[1], how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
23. Made you feel sad, discouraged, or hopeless?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
24. Made you feel down hearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
25. Made you feel wiped out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
26. Caused you to be concerned or worried about your health?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
27. Caused you to plan activities more carefully?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
28. Made you feel inconvenienced about always carrying extra pads, tampons, and clothing to avoid accidents?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
29. Caused you embarrassment?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
30. Made you feel uncertain about your future?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
31. Made you feel irritable?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
32. Made you concerned about soiling outer clothes?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
33. Affected the size of clothing you wear during your periods?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
34. Made you feel that you are not in control of your health?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
35. Made you feel weak as if energy was drained from your body?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
36. Diminished your sexual desire?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
37. Caused you to avoid sexual relations?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix 4 PGIC (Patient Global Impression of Change)

1) Very much improved
2) Much improved
3) Minimally improved
4) No change
5) Minimally worse
6) Much worse
7) Very much worse