A Randomized, Multicenter, Double-Blind, Placebo-Controlled Phase 2 Study to Evaluate the Safety and Efficacy of HMI-115 in Women with Moderate to Severe Endometriosis-Associated Pain Over a 12-Week Treatment Period

Short Title:	To evaluate the safety and efficacy of HMI-115 in women with moderate to severe endometriosis-associated pain over a 12-week treatment period
Compound:	HMI-115
Indication:	Moderate to Severe Endometriosis-Associated Pain
Study Sponsor:	Hope Medicine (Nanjing) Co. Ltd.
Protocol Number:	HMI-115EM201
Study Phase:	Phase 2
Vision number:	6.0
Approval Date:	April 11, 2024

Amendment summary

Version	Date	Main Changes/ Reasons
1.0	April 21, 2021	Not applicable
2.0	August 12, 2021	Screening Period, Schedule Of Activities, Inclusion and Exclusion Criteria, Discontinuation of IMP and Subject Withdrawal, Definition of AESI, Contraceptive Guidance.
3.0	November 23, 2021	Schedule Of Activities, Inclusion and Exclusion Criteria, Discontinuation of IMP, Subject Withdrawal from the Study, window period for DXA, Pregnancy, Primary and Secondary Efficacy Endpoints assessment, Recording and Follow up of AE and SAE, Contraceptive Guidance.
3.1	April 14, 2022	Coagulation sampling time, study region, Inclusion and Exclusion Criteria, Rescue Medicines, Prohibited Medications, Analyses Set, Estimand, Definition of AESI.
3.2	April 26, 2022	Modified the name of CMO
4.0	March 03, 2023	Modified the inclusion criteria and exclusion criteria, Prohibited Medications, Estimand, Definition of AESI, schedule of activity, etc.
5.0	September 20, 2023	Deleted planned part 2 of the study, added an interim analysis, revised DXA follow-ups, etc.

Version	Date	Main Changes/ Reasons
6.0	April 11, 2024	Added some notes for the clinical operation, added a second interim analysis, wording change to avoid ambiguity.

[redacted]

11-Apr-2024 | 16:46 CST

Date

Medical Monitor Name and Contact Information:

[redacted]

11-Apr-2024 | 16:49 CST

Date

Table of Contents

List of Figures

List of Tables

1 Protocol Summary

1.1 Synopsis

Protocol Title: A Randomized, Multicenter, Double-Blind, Placebo-Controlled Phase 2 Study to Evaluate the Safety and Efficacy of HMI-115 in Women with Moderate to Severe Endometriosis-Associated Pain Over a 12-Week Treatment Period

Sponsor Protocol No.: HMI-115EM201

Study Phase: Phase 2

Sponsor: Hope Medicine (Nanjing) Co. Ltd

Rationale:

A First-in-Human (FiH) study with HMI-115 has already established the safety and tolerability of HMI-115 when administered subcutaneously in post-menopausal women aged between 45 to 65 years in single doses up to 240 mg and multiple doses up to 90 mg once every two weeks (Q2W) for 6 weeks.[1]This study aims to evaluate the safety and efficacy of HMI-115 versus a placebo in pre-menopausal women aged 18 to 49 years diagnosed with moderate to severe endometriosis associated pain. The study will determine the safety and efficacy of HMI-115 at 60 mg Q2W, 120 mg Q2W, and 240 mg Q2W.

Objectives and Endpoints:

Objectives	Endpoints
Primary To study the efficacy of HMI-115 for 12 weeks compared with placebo in the management of endometriosis-associated pain	**Primary** Change in dysmenorrhea (DYS) measured by Numeric Rating Scale (NRS) from Baseline to Week 12
Secondary To study the safety, tolerability, and persistence of efficacy of HMI-115 compared with placebo	**Secondary** **<u>Efficacy</u>** 1. Change in DYS measured by NRS from Baseline to Week 24 2. Change in non-menstrual pelvic pain (NMPP) measured by NRS from Baseline to Week 12 and 24 3. Change in dyspareunia (DYSP) measured by NRS from Baseline to Week 12 and 24

Objectives	Endpoints
	4. Change from Baseline (CFB) in the monthly mean Endometriosis Daily Impact Pain Scale for DYS, NMPP and DYSP at Week 12 and 24 5. CFB by visit in permitted rescue medication use 6. Change in menstrual period heaviness (bleeding) from Baseline by visit **Safety and tolerability** 1. Adverse events (AEs) 2. CFB by visit in vital signs (blood pressure [BP], pulse, body temperature, and respiratory rate [RR]) 3. CFB by visit in physical examinations 4. Number and ratio of participants used concomitant medication 5. CFB by visit in twelve-lead electrocardiogram (ECG) 6. CFB by visit in clinical laboratory tests (hematology, coagulation, clinical chemistry, urinalysis, hormones and CA-125) 7. CFB in Bone mineral density by Dual energy X-ray absorptiometry (DXA) scan after 12 weeks' treatment (at EOT visit) 8. CFB in transvaginal ultrasound (TVU) index (including number and size of ovarian cyst, thickness of endometrium) after 12 weeks' reatment (at EOT visit)
Exploratory To explore the effect of HMI-115 on Quality of Life, pharmacokinetics (PK), PK-PD relationship and immunogenicity	**Other patient-reported outcomes:** 1. Quality of Life assessment with health-related quality of life questionnaire (HRQoL) (Endometriosis Health Profile-5 [EHP-5]) 2. Response to Patient Global Impression of Change (PGIC) **PK** 1. C_{max}, C_{min}, t_{max}, $AUC_{(0\text{-}tau)}$, $t_{1/2}$ following last dose

Objectives	Endpoints
	2. Accumulation ratio (AR) for both C_{max} and AUC **PK-PD** Relationship between HMI-115 plasma concentration/exposure and pelvic pain score measured by NRS (cyclic = DYS, non-cyclic = NMPP+DYSP, and average)/side effects **Immunogenicity:** Anti-drug antibody (ADA)

Overall Design: This is a Phase 2, multicenter, double-blind, placebo-controlled, randomized study to assess the safety and efficacy of HMI-115 subcutaneously administered monoclonal antibody versus placebo in pre-menopausal women with moderate to severe endometriosis-associated pain. The study will comprise of three periods (refer to Figure 1-1):

1) A **Screening Period** of up to 75 days prior to first dose:
   - Screening Visit 1
   - Screening Visit 2 (at least 35 days before V3 to ensure at least 5 weeks baseline pain score obtained before randomization)
2) A **Treatment Period** (12 weeks). Subjects will be given subcutaneous (s.c.) injections Q2W in the study.
3) A **Follow-up Period** of 12 weeks

Number of Subjects:

152 eligible subjects will be randomly assigned to HMI-115 or placebo and 136 evaluable subjects for an estimated total of 34 evaluable subjects per treatment group.

Intervention Groups and Duration:

Eligible subjects will be randomized into four arms: placebo, 60 mg, 120 mg, and 240 mg HMI-115 in a 1:1:1:1 ratio with 38 subjects/arm.

Blood samples will be collected to determine PK profile from Day 1 to Day 169. A full PK sampling strategy will be followed for a subgroup of 10 subjects per arm (refer to Table 1-2). Sparse sampling will be obtained from the rest of the subjects (refer to Table 1-3). Intensive and

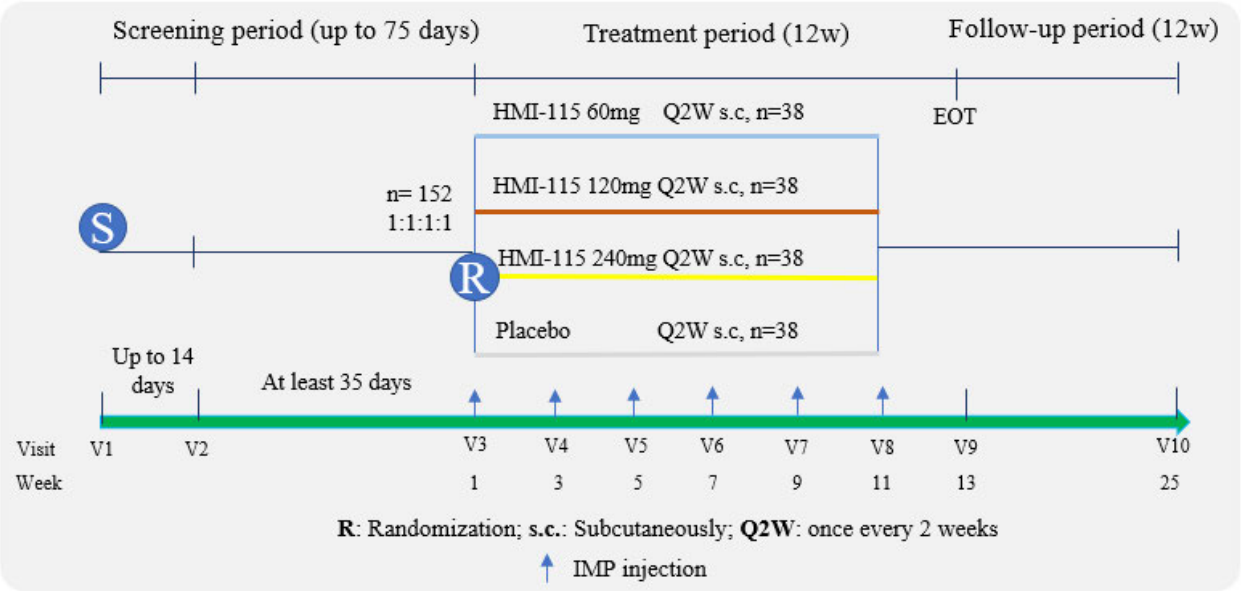
sparse PK blood sampling will be performed at timepoints specified in Table 2 and Table 3. Plasma concentrations of HMI-115 will be determined using a validated enzyme-linked immunosorbent assay (ELISA) method. PK parameters will be assessed as described in Section 9.4.9.

An e-Diary will be dispensed, and training will be provided to subjects at Visit 2 on how to record endometriosis associated pain, uterine bleeding, and analgesic medication use for endometriosis associated pain on a daily basis. Study related examinations, laboratory assessments and pregnancy testing will be performed according to the schedule of activities (SoA) throughout the study (refer to Table 1-1).

Data Monitoring Committee (DMC) will be used for this study.

1.2 Schema

Figure 1–1: Study Design for Part 1 of the Study



1.3 Schedule of Activities (SoA)

Table 1-1 SoA for the study

Procedure	Screening Period Up to 75 days prior to the first dose		Treatment Period						EOT[4*]	Follow-up Period[5*]
Date	Screening Visit 1[1] Up to 14 days prior to V2	Screening Visit 2[2] At least 35 days prior to V3	Week 1 (Day 1)[3]	Week 3 (Day 15 ±3)	Week 5 (Day 29 ±3)	Week 7 (Day 43 ±3)	Week 9 (Day 57 ±3)	Week 11 (Day 71 ±3)	Week 13 (Day 85 ±2/4)	Week 25 (Day 169 ±7)
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Informed consent	X									
Inclusion and exclusion criteria	X	X	X							
Demographics	X									
Medical history, current medical conditions	X									
Prior medications	X									
Height (cm) and weight (kg)[6]	X		X		X		X		X	X
BMI (kg/m^2)	X									
CPSSS assessment	X								X	
Randomization			X							
IMP administration and observe x 1 hour[7]			X	X	X	X	X	X		
Urine drug screen[8]	X									
Pregnancy test[9]	X		X		X		X		X	X
Mammogram[10]	X									
Cervical cytology[11]	X									
DXA scan[12]	X								X[13]	
Sellar MRI with contrast[12]	X									
TVU[14]	X								X	

Procedure	Screening Period Up to 75 days prior to the first dose		Treatment Period						EOT[4*]	Follow-up Period[5*]
Date	Screening Visit 1[1] Up to 14 days prior to V2	Screening Visit 2[2] At least 35 days prior to V3	Week 1 (Day 1)[3]	Week 3 (Day 15 ±3)	Week 5 (Day 29 ±3)	Week 7 (Day 43 ±3)	Week 9 (Day 57 ±3)	Week 11 (Day 71 ±3)	Week 13 (Day 85 ±2/4)	Week 25 (Day 169 ±7)
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Viral Serology[15]	X									
Hematology, clinical chemistry, coagulation and urinalysis[16]	X		X		X		X		X	
FT3, FT4, TSH, GH and CA 125[16]	X		X		X		X		X	X
Bone biomarkers (CTX, P1NP, BSAP)[16]			X						X	
Sex hormone: PRL, LH, FSH, estradiol, progesterone, testosterone, DHEAS[16]	X		X		X[17]		X[17]		X[17]	X[17]
eGFR[18]	X								X	
12-lead ECG[19]	X	X	X	X	X	X	X	X	X	X
Vital signs[20]	X	X	X	X	X	X	X	X	X	X
Complete physical examination[21]	X								X	X
Brief physical examination[21]		X	X	X	X	X	X	X		
Pelvic examination[22]	X								X	
e-Diary[23]		X	X[24]	X[24]	X[24]	X[24]	X[24]	X[24]	X[24]	X[24]
Rescue medication prescription[25]		X	X	X	X	X	X	X	X	
AE monitoring	X	X	X	X	X	X	X	X	X	X
Injection site reaction[26]			X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X

Procedure	Screening Period Up to 75 days prior to the first dose		Treatment Period						EOT[4*]	Follow-up Period[5*]
Date	Screening Visit 1[1] Up to 14 days prior to V2	Screening Visit 2[2] At least 35 days prior to V3	Week 1 (Day 1)[3]	Week 3 (Day 15 ±3)	Week 5 (Day 29 ±3)	Week 7 (Day 43 ±3)	Week 9 (Day 57 ±3)	Week 11 (Day 71 ±3)	Week 13 (Day 85 ±2/4)	Week 25 (Day 169 ±7)
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
PGIC					X		X		X	X
EHP-5			X		X		X		X	X
ADA sampling[27]			X	X	X		X		X	X
PK sampling[28]			X	X	X		X	X	X	X

Abbreviation: ADA = anti-drug antibody; AE = adverse event; anti-HAV = hepatitis A virus antibody; anti-HIV = human immunodeficiency virus antibodies; ASCUS = atypical squamous cells of undetermined significance; BMI = body mass index; BSAP = bone specific alkaline phosphatase; CA-125 = cancer antigen-125; CPSSS= Composite pelvic signs and symptoms score; CTX = C-terminal telopeptide of type 1 collagen; DXA = dual energy X-ray absorptiometry; DHEAS = Dehydroepiandrosterone-sulfate; ECG = electrocardiogram; e-Diary: Electronic Diary, EHP-5 = Endometriosis Health Profile-5; EOT = end of treatment; FSH = follicle-stimulating hormone; FT3= Free triiodothyronine; FT4= Free thyroxine; eGFR = estimated glomerular filtration rate; GH=growth hormone; HBsAg = hepatitis B virus surface antigen; HBcAb = Hepatitis B core antibody; HCV = hepatitis C virus; LH = luteinizing hormone; IMP = investigational medicinal product; MRI = magnetic resonance imaging; P1NP = procollagen type 1N-terminal propertied; PGIC = Patient Global Impression of Change; PK = Pharmacokinetics; PRL = Prolactin; PVC = Premature ventricular contractions; Q2W = once every 2 weeks; QTcF =QT interval corrected for heart rate using Fridericia's correction formula ; RNA = ribonucleic acid; V = Visit; TSH = thyroid stimulating hormone; TVU = transvaginal ultrasound.

1. The time interval between Screening Visit 1 and Screening Visit 2 is no longer than 14 days. Specific procedures listed for Visit 1 could be scheduled during this period.
2. At Screening Visit 2, e-Diary will be dispensed. The time interval between Visit 2 and Visit 3 will at least cover a 35-day baseline period.
3. Day 1 should start from the menses cycle days 1 to 5. Data obtained from Day 1 will be utilized as baseline for analysis (except for e-Diary data).
4. The EOT Visit should be 14 days from the last dose of IMP (Visit 8). The time window of EOT visit is dependent on the schedule of the PK subgroup (intensive PK, ±2 days, sparse PK, ±4 days). The arrangement for TVU, pelvic examination or lab tests could be based on menses cycle.
5. Refer to Section 7.1 and 7.2 for the follow-up requirement for subjects who discontinue from IMP or withdraw from the study.
6. Height at Screening Visit 1 only.
7. IMP will be administered Q2W after collecting all testing/examination data at each visit (refer to #20 for additional vital signs at Visit 3). Subjects will be monitored for 1 hour at the site after dosing.
8. Urine drug screen includes amphetamine, barbiturates (except for sites in China), benzodiazepines, tetrahydrocannabinol, cocaine, methadone, methamphetamine, opiates, phencyclidine, and tricyclic antidepressants (except for sites in China).
9. Serum pregnancy test at Visit 1 only, and urine pregnancy test at Visits 3, 5, 7, 9 and 10. Negative result must be obtained prior to randomization at Visit 3.
10. Mammogram for females aged 40 and over only (can be performed at any time during screening period), unless mammography or MRI were performed with normal results within 12 months prior to randomization.

11. Cervical cytology can be assessed at any time during the Screening period. (Virgins may be exempted per the investigator's discretion)
12. DXA scan and Sellar MRI can be assessed at any time during the Screening period. Only subjects who have greater chances of enrollment into the study will undergo DXA scan and Sellar MRI. For subjects who are eligible for randomization, the Screening DXA data will be used as baseline.
13. Subjects who discontinue from IMP prior to week 11 or become pregnant during the study does not require a DXA scan. For more details, including subjects who needs further DXA scan after EOT visit, refer to Section 8.2.7.
14. TVU should be performed during the early proliferative phase of the subject's menstrual cycle (approximately days 4 through 8). In some circumstances, transrectal or transabdominal ultrasound is allowed per the investigator's discretion.
15. Viral serology tests include anti-HAV, HBsAg, HBcAb, anti-HCV, HCV RNA (for positive or equivocal anti-HCV), and HIV antigen/anti-HIV (1+2).
16. Clinical laboratory tests are listed in Section 10.2. Samples of sex hormones (PRL, LH, FSH, estradiol, progesterone, testosterone, DHEAS) will be collected at the menses cycle days 1 to 5, and **subjects should not take any opioids 2 days prior to blood sampling of PRL**.
17. Blood samples of sex hormones (PRL, LH, FSH, estradiol, progesterone, testosterone, DHEAS) could be taken on a separate day from the scheduled Visit Day to meet the menses cycle days 1 to 5.
18. eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) formula.
19. 12-ECG can be tested at any time apart from the specified timepoints if the subject feels uncomfortable. If QTc prolongation is found, including repeating PVCs confirmed by additional ECG examination at least 30 minutes apart, or QTcF >500 ms, or increase in QTcF interval >60 ms compared to baseline in the absence of possible causes other than the IMP, drug can be temporarily stopped to investigate the reason. See Section 7.1 for more details.
20. Vital signs include blood pressure, tympanic body temperature, pulse, and respiratory rate. Vital signs of subjects will be observed 1 hour after IMP administration on Day 1 and pre-dose at each visit.
21. Physical examination: for detailed information, refer to section 8.2.1.
22. Pelvic examination: for detailed information, refer to section 8.2.3 and 10.9.
23. e-Diary training will be provided at Visit 2, and e-Diary will be dispensed to record endometriosis associated pain (including NRS and scales for DYS, NMPP and DYSP), uterine bleeding, and rescue medication use for endometriosis associated pain on a daily basis from Visit 2 and at approximately the same time every day (morning preferred). Must be completed in the morning prior to arrival at the study site for study visits.
24. e-Diary entries compliance will be assessed and additional training will be provided to subjects who have missed data entry.
25. Rescue medication and education will be provided to subjects from Visit 2 for rescue use if needed for endometriosis associated pain throughout the study. Refer to table 6-3 for protocol allowed rescue medication.
26. All reported AEs to be checked for injection site reaction.
27. In addition to the listed sampling time, ADA will also be collected at week 17, together with PK sampling (not required for those who discontinued from IMP or withdraw from study).
28. Intensive and sparse PK blood sampling will be performed at timepoints specified inTable 1-2 and Table 1-3.

Note: Blood draws should be performed before vital signs, ECG recordings and physical examinations at visits (can be adjusted according to the condition of the site).

A certified central laboratory will be utilized to process and provide results for all blood tests.

DXA will be analyzed/evaluated centrally by an experienced and qualified imaging vendor.
Procedures that allowed to be repeated during screening period are listed in section 10

Table 1-2 Intensive PK Subset (N=10 per arm)

WEEK	STUDY DAY	TIME (in relation to dosing)		TIME WINDOW
		hour	day	
Week 1	Day 1(first dose)	Pre-dose	Pre-dose	
Week 1	Day 3	+48 h (post-first dose)	+2 day (post-first dose)	+/-2 h
Week 1	Day 5	+96 h (post-first dose)	+4 day (post-first dose)	+/-2 h
Week 1	Day 7	+144 h (post-first dose)	+6 day (post-first dose)	+/-6 h
Week 2	Day 11	+240 h (post-first dose)	+10 day (post-first dose)	+/-12 h
Week 3	Day 15±3	Pre-dose	Pre-dose	Within 2 h before dosing
Week 5	Day 29±3	Pre-dose	Pre-dose	Within 2 h before dosing
Week 9	Day 57±3	Pre-dose	Pre-dose	Within 2 h before dosing
Week 11	Day 71±3(last dose)	Pre-dose	Pre-dose	Within 2 h before dosing
Week 11	Day 73	+48 h (Post-last dose)	+2 day (Post-last dose)	+/-2 h
Week 11	Day 75	+96 h (Post-last dose)	+4 day (Post-last dose)	+/-2 h
Week 11	Day 77	+144 h (Post-last dose)	+6 day (Post-last dose)	+/-6 h
Week 12	Day 81	+240 h (Post-last dose)	+10 day (Post-last dose)	+/-1 day
Week 13	Day 85	+336 h (Post-last dose)	+14 day (Post-last dose)	+/-2 days
Week 17	Day 113	+ 1008 h (Post-last dose)	+42 day (Post-last dose)	+/-7 days
Week 19	Day 127	+1344 h (Post-last dose)	+56 day (Post-last dose)	+/-7 days
Week 21	Day 141	+ 1680 h (Post-last dose)	+70 day (Post-last dose)	+/-7 days
Week 25	Day 169	+ 2352 h (Post-last dose)	+98 day (Post-last dose)	+/-7 days

Table 1-3 Sparse PK Sampling

WEEK	STUDY DAY	TIME (in relation to dosing)		TIME WINDOW
		hour	day	
Week 1	Day 1(first dose)	Pre-dose	Pre-dose	
Week 1	Day 7	+144 h (post-first dose)	+6 (post-first dose)	+/-2 days
Week 3	Day 15±3	Pre-dose	Pre-dose	Within 2 h before dosing
Week 5	Day 29±3	Pre-dose	Pre-dose	Within 2 h before dosing
Week 9	Day 57±3	Pre-dose	Pre-dose	Within 2 h before dosing
Week 11	Day 71±3(last dose)	Pre-dose	Pre-dose	Within 2 h before dosing
Week 11	Day 77	+144 h (post-last dose)	+6 day (post-last dose)	+/-2 days
Week 13	Day 85	+336 h (post-last dose)	+14 day (post-last dose)	+/-4 days
Week 17	Day 113	+ 1008 h (post-last dose)	+42 day (post-last dose)	+/-7 days
Week 25	Day 169	+ 2352 h (Post-last dose)	+98 day (Post-last dose)	+/-7 days

Note: For subjects discontinued from IMP or withdraw from study, no additional PK sampling except for EOT and EOS visits (if possible) is required after IMP discontinuation.

2 Introduction

HMI-115 is a highly specific human monoclonal antibody that will be investigated for safety and efficacy in pre-menopausal women with moderate to severe endometriosis associated pain.

2.1 Study Rationale

A First-in-Human (FiH) study with HMI-115 has already established the safety and tolerability of HMI-115 when administered subcutaneously in post-menopausal women aged between 45 to 65 years in single doses up to 240 mg and multiple doses up to 90 mg once every 2 weeks (Q2W) for 6 weeks[1]. This study aims to evaluate the safety and efficacy of HMI-115 versus a placebo in pre-menopausal women aged 18 to 49 years diagnosed with moderate to severe endometriosis associated pain. The study will determine the safety and efficacy of HMI-115 at 60 mg Q2W, 120 mg Q2W, and 240 mg Q2W. Administration of different doses of HMI-115 together with placebo will allow for further evaluation of efficacy and safety of the drug and determine appropriate dose for future pivotal studies.

As a prove-of-concept study, change in dysmenorrhea (DYS) is used as the primary endpoint to show the preliminary efficacy of HMI-115 in endometriosis associated pain. Non-menstrual pelvic pain (NMPP) is considered as critical endometriosis associated pain, and is used for recruiting subjects with Composite Pelvic Signs and Symptoms Score (CPSSS) at least 2 for NMPP and evaluating NMPP by NRS as a secondary endpoint. Co-primary endpoints include DYS and NMPP would be used in the confirmative studies in future. In addition, a central laboratory will be used in this study for blood tests (including hormones). Dual energy X-ray absorptiometry (DXA) scan, as a bone mineral density (BMD) monitoring indicator, will be performed with a central reading. Transvaginal ultrasound (TVU), mainly to confirm the eligibility for study entry and to assess the condition of pelvis after administration of HMI-115, are suggested to be performed by the same staff from each site. Sellar MRI with contrast will also be performed locally for excluding subjects with pituitary tumor growth.

This study will not recruit subjects with obvious pre-existing mood disorders such as depression, bipolar disorder, besides, HMI-115 has not shown any potential of affecting subjects' mental state based on the mechanism of action, therefore, the mood state assessment by tools will not be involved at the current stage. However, if any sign of mental influence of HMI-115 is detected, a validated tool such as the Columbia-Suicide Severity Rating Scale will be used in the future studies.

2.2 Background

Endometriosis is a gynecological disorder that manifest during the reproductive years of women with initial symptoms seen during adolescence. However, these initial symptoms may be very mild

leading to the condition being undiagnosed for a long time. The pathophysiology of the disorder is yet to be fully understood but the disease is an estrogen dependent inflammatory condition that involves the formation of endometrial tissue outside the uterine cavity.

The prevalence of endometriosis has been reported to be around 10 % of reproductive aged women[2]. In population-based studies, the annual incidence of endometriosis has been reported to be 0.1 % to 0.3 %[3,4,5,6]. Thus, endometriosis is one of the most common gynecologic conditions. The symptoms of endometriosis have a tremendous impact on patients' lives, negatively influencing quality of life, fertility, emotional well-being, intimate relationships, work life, and daily activities.

As endometriosis is estrogen-dependent, drugs interfering negatively with estradiol-mediated signaling such as gonadotropin-releasing hormone (GnRH) agonists and antagonists as well as antiestrogens, selective estrogen receptor modulators (SERMs) and aromatase inhibitors proved to be effective in human endometriosis. Surgery is another optional treatment method for endometriosis but has drawbacks. Because of the characteristics of the disease itself, it is difficult to remove all the lesions through surgery, so the recurrence of the disease is very common. Plus, there is the risk of surgical complications, which make surgical treatment more challenging. According to statistics, the 2-year recurrence rate post-surgery of endometriosis is 21.5%, and the 5-year recurrence rate is 40-50%[7]. Long-term medication treatment is necessary and routine practice to prevent relapse post-surgery. Many available drugs for endometriosis induced "amenorrhea" conflicts with patient' s desire for fertility. Many of these treatments have significant side effects and/or precaution (such as hot flushes, bone loss, venous thromboembolism, and contraindicated with history of diabetes) or may not provide adequate pain relief, leading to non-adherence to long term treatment. Historically, these treatments have not been effective at resolving high endometriosis relapse rates. Endometriosis is a chronic serious disease with no viable long term treatment options. Therefore, there is an unmet medical need for a safe and effective long term endometriosis therapy.

It had reported that prolactin (PRL) and its receptors are overexpressed in endometriotic tissue. There is evidence that systemic hyperprolactinemia can cause endometriosis in women. Systemic administration of bromocriptine reduces serum PRL level, and vaginal application of bromocriptine alleviates pain and menstrual bleeding in women with interna endometriosis. Prolactin signalling may be involved in the pathophysiology of endometriosis by (a) systemic hyperprolactinemia (b) disease-associated organ-specific overexpression or constitutively active mutations of the prolactin receptors (PRLR) or (c) local hyperprolactinemia via autocrine or paracrine mechanism (refer to the Investigator's Brochure [IB]). PRLR antagonists provide new insight to resolve unmet medical needs in the treatment of endometriosis.

In mammals (including humans), the PRLR is widely distributed. PRLR antagonists may act in many different tissues, its safety needs to be evaluated. But according to Newey et al. who reported the first loss-of-function mutation of the PRLR in family hyperprolactinemia (i.e., excess of circulating PRL) in 2013, one should expect that drug mediated down-regulation of systemic PRLR-signaling in patients should exert no major interference with any physiological function other than female fertility[8].

The possible advantage of PRLR antagonists includes absence of side effects of drugs interfering negatively with estradiol-mediated signaling, no restriction of the targeted population, and non-proliferative action on the breast epithelium as opposed to estrogens and progestins. Of interest, PRLR antagonists prevented/reversed PRL effects involving TRPV1 which are considered as potential targets in the treatment of inflammatory pain. It has potential to relieve pain and opioid-induced hyperalgesia (OIH) in female selectively by limiting PRL/PRLR-S signaling pharmacologically[9,10].

BAY1158061 is a highly specific human monoclonal antibody that was developed by Bayer HealthCare AG to treat endometriosis. This product was acquired by Hope Medicine (Nanjing) Co., Ltd and its parent company Hope Medicine Inc., and is now known by the name HMI-115.

HMI-115 binds to the extracellular domain of the PRLR leading to diminished PRLR signaling. In a PRL driven murine endometriosis interna model, the parental lead antibody and HMI-115 in the murine IgG2a format showed full efficacy in treating interna endometriosis. In the FiH study that aimed at establishing the safety and tolerability of HMI-115 in single doses up to 240 mg and cumulative doses up to 270 mg (3×90 mg) in healthy post-menopausal female subjects, HMI-115 was well tolerated in all doses.[1] No significant impact of HMI-115 on the sex hormone levels (e.g., estrogen) have been observed. The FiH study showed a favorable safety profile and full efficacy was observed in preclinical studies thereby providing a new approach to resolve unmet medical needs in the treatment of endometriosis.

Pharmacokinetic (PK) evaluation of HMI-115 demonstrated that the drug reached peak plasma concentration approximately 4 to 11 days after administration of 7.5 mg to 240 mg subcutaneously. Following repeated dosing and an accumulation index of approximately 2, a more than dose proportional increase in the main PK parameters was observed. Pharmacodynamic (PD) evaluation of HMI-115 demonstrated no effect on the circadian rhythm of PRL secretion.[1]

HMI-115 was well tolerated in FiH studies and animal studies. In post-menopausal women, no specific adverse events (AE) patterns or clinically significant effects on the vital signs, ECG or laboratory parameters were observed. As a fertility and early embryonic study in female

Cynomolgus monkeys demonstrated that weekly administration of HMI-115 at doses up to 50 mg/kg prior to mating, throughout mating and post-mating/early gestation did not affect the mating success and had no influence on pregnancy outcome, this study will further evaluate the safety and efficacy of HMI-115 in pre-menopausal women with endometriosis related pain.

A detailed description of the chemistry, non-clinical pharmacology and toxicology data for HMI-115 is provided in the most updated version of IB.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of HMI-115 may be found in the IB of HMI-115.

2.3.1 Risk Assessment

Table 2-1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
HMI-115		
Non-clinical Risks Pituitary gland function (endocrinology)	Nonclinical - toxicology studies in monkeys demonstrated HMI-115 to elevate PRL levels which may influence other hormone levels. In the 26-week toxicity study in male and female cynomolgus monkeys treated with 24 and 100 mg/kg of HMI-115 weekly, no HMI-115 related changes were noted in hormone detection (testosterone, estradiol and progesterone) throughout the study.	In the FiH study, the hormone TSH, cortisol, somatotropin, FSH, LH, and estradiol were evaluated and no significant changes observed in the doses tested. The hormonal levels will be monitored in this study as higher doses of HMI-115 will be administered. The impact of treatment with HMI-115 on other hormones remains to be investigated further
Non-Clinical Risk Mammary gland function	Toxicology studies in Cynomolgus monkeys showed a minimal reversible atrophy of the mammary gland	Changes in mammary gland function is reversed after a dosing-free period. Treatment contraindicated during pregnancy and lactation and in women with abnormal clinical findings during mammography

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Clinical Risk Immune function	Neutropenia was reported in one subject in the Phase 1 study (subject already had a neutrophil count that was lower than the lower limit of normal [LLN] prior to enrollment)	Careful monitoring of subjects for any ongoing, subclinical infection and exclusion of patients with existing immunosuppression.
Non-Clinical Risk Cardiovascular system	Slight increase in single ectopic ventricular heart beats in Cynomolgus monkey at highest tested dose (At the No Observed Adverse Effect Level (NOAEL) in the cardiovascular safety study there is an 11-fold safety margin for the 240 mg Q2W dose based on C_{max}).	Monitoring of electrocardiographic parameters through ECG measurements.
Clinical Risk PRLR blockade may induce PRL over secretion. Whether it affects secretion of other sex hormones and dopamine through the Hypothalamic-Pituitary axis feedback is unknown. Considering PRLR is blocked, PRL effect on other hormones is very likely to be minimized.	Increased PRL may cause disorder in the secretion of other sex hormones and dopamine and further induce conditions such as galactorrhea, change in menstrual cycles with oligo- or amenorrhea, hirsutism, acne, change in mood, etc. However, considering the blockade of PRLR by HMI-115, the above conditions are very unlikely to be induced by HMI-115.	Collect galactorrhea, change in menstrual cycles with oligo- or amenorrhea, Hirsutism, Acne, change in mood, etc., as adverse event of special interests (AESIs). Refer to Section 10.3.1.
Non-Clinical Risk Bone cell metabolism	Loss of bone mineral density in PRLR knock-out mice. Biomarkers of bone formation/resorption (CTX-1; t-P1PNP, PTH) and bone mineral densitometry were investigated in GLP-toxicity studies that involved administration of HMI-115 in Cynomolgus monkeys and no adverse impact was identified	Monitoring by CTX, P1NP, BSAP and DXA scan. Refer to Section 8.2.7 for details on DXA scan.
Study Procedures		
HMI-115 will be administered by injection through s.c. route in the study. The subjects will receive	Application site reaction such as swelling, hematoma, and pain. Repeated s.c. injections may cause	Local tolerability studies and HMI-115's low to medium immunogenicity indicate s.c. route of administration does not cause

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
injections of HMI-115 (60 mg to 240 mg) or placebo.	inconvenience to subjects and make injection site assessments difficult. However, according to 26-week toxicity study in male and female cynomolgus monkeys, there were minimal or mild non-adverse microscopic findings (subcutaneous and/or intramuscular mixed cell inflammation) in the injection sites.	any site reaction that is outside normal range. However, due to repeated s.c. injections over 12 weeks in the study, injection sites need to be sufficiently apart from each other to allow for injection site assessments.

2.3.1.1 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

There is currently an outbreak of respiratory disease (COVID-19) caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The countermeasures initiated by national and local governments worldwide and the recommendations issued by the health authorities have impacted current and new clinical studies. As the threat of pandemic burden including new outbreaks, locally or globally, will impact the further conduct of clinical studies, appropriate risk assessments and mitigation measures will need to be taken into consideration in all clinical studies to protect subjects, site staff and society as a whole.

Both European Medicines Agency (EMA)[11] and United States Food and Drug Administration (USFDA)[12] have issued new guidelines that aim to provide recommendations for the conduct of clinical studies of medical products during COVID-19 pandemic. Since the pandemic situation is evolving, guidelines, recommendations, national laws and local restrictions may change at a rapid pace.

Appropriate measures have been implemented into this protocol to conduct the study.

Risk Assessment for COVID-19 Pandemic

HMI-115 is not believed to cause immune suppression. Therefore, risk of the subjects to COVID-19 will be similar to the general population. However, the risk of exposure to infected people cannot be completely excluded as the subjects may be exposed to public areas (e.g., commute to the site) and have additional human contact (e.g., with site staff and other subjects of the clinical study).

Measures to mitigate the additional risks caused by COVID-19 include:

- This study will start enrolling only when both the Sponsor and Contract research organization (CRO) agree that it is safe to start the study.

- Current national laws and local recommendations to prevent further spread of COVID-19 will be strictly adhered to.
- Subjects will be closely monitored for any signs and symptoms of COVID-19, including fever, dry cough, dyspnea, sore throat and fatigue throughout the study. Once clinical signs of infection are reported by subjects, the Investigator needs to determine whether samples can be collected, and safety data can be recorded on site. If not, AE and concomitant medications will be obtained via phone calls. Daily tympanic body temperature measurements during in-house stay and outpatient visits will be implemented.
- The IMP will not be administered to subjects upon identification of any signs of COVID-19 infection.
- Confirmation of COVID-19 infection by optional laboratory assessment will be conducted based on Investigator's discretion and/or local requirements and/or policy.
- The probability of virus transmission will be controlled as much as possible by:
    - Advising subjects to adhere to local requirements for reduction of the public exposure while ambulatory.
    - All subjects are contacted by phone one day prior to every visit for assessing COVID-19 symptoms and signs and are asked not to attend the site in case of suspected infection reported. If applicable, subjects will be referred to the local health care system for further follow up and treatment.
    - Physical distancing and person-to-person contact restrictions will be applied during on-site visits.
    - Where physical distancing is not possible, personal protective equipment (PPE) will be used by study subject (surgical face mask, gloves) and staff (for example, but not limited to masks, gloves, protectors, medical suits) if deemed appropriate by the Investigators and site staff and guided by local requirements.

The measures may be adjusted according to local laws and/or policy.

2.3.2 Benefit Assessment

HMI-115 may have the potential benefit of relieving moderate to severe pain caused by endometriosis and improve the Health-related Quality of life (HRQoL) of patients with endometriosis. For details on dose justification of this study, refer to Section 4.3. Clear criteria for subject selection and close monitoring of identified potential risks and subject discontinuation have been implemented in this protocol to avoid undue risks to the subjects. An independent data monitoring committee (DMC) will regularly review all safety data to ensure the well-being of all subjects.

2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with HMI-115 are justified by the anticipated benefits that may be afforded to subjects with endometriosis associated pain.

3 Objectives and Endpoints

Table 3-1. Objectives and Endpoints

Objectives	Endpoints
Primary To study the efficacy of HMI-115 for 12 weeks compared with placebo in the management of endometriosis associated pain	**Primary** Change in dysmenorrhea (DYS) measured by Numeric Rating Scale (NRS) from Baseline to Week 12
Secondary To study the safety, tolerability, and persistence of efficacy of HMI-115 compared with placebo	**Secondary** **<u>Efficacy</u>** 1. Change in DYS measured by NRS from Baseline to Week 24 2. Change in non-menstrual pelvic pain (NMPP) measured by NRS from Baseline to Week 12 and 24 3. Change in dyspareunia (DYSP) measured by NRS from Baseline to Week 12 and 24 4. Change from Baseline (CFB) in the monthly mean Endometriosis Daily Impact Pain Scale for DYS, NMPP and DYSP at Week 12 and 24 5. CFB by visit in permitted rescue medication use. 6. Change in menstrual period heaviness (bleeding) from Baseline by visit **<u>Safety and tolerability</u>** 1. Adverse events (AEs) 2. CFB by visit in vital signs (blood pressure [BP], pulse, body temperature, and respiratory rate [RR]) 3. CFB by visit in physical examinations 4. Number and ratio of paticipants used concomitant medication 5. CFB by visit in twelve-lead electrocardiogram (ECG)

Objectives	Endpoints
	6. CFB by visit in clinical laboratory tests (hematology, coagulation, clinical chemistry, urinalysis, hormones and CA−125) 7. CFB in bone mineral density by Dual energy X-ray absorptiometry (DXA) scan after 12 weeks' treatment (at EOT vist) 8. CFB in transvaginal ultrasound (TVU) index (including number and size of ovarian cyst, thickness of endometrium) after 12 weeks' treatment (at EOT visit)
Exploratory To explore the effect of HMI-115 on Quality of Life, pharmacokinetics (PK), PK-PD relationship, and immunogenicity	**Other patient-reported outcomes:** 1. Quality of Life assessment with health-related quality of life questionnaire (HRQoL) (Endometriosis Health Profile-5 [EHP-5]) 2. Response to Patient Global Impression of Change (PGIC) **PK** 1. C_{max}, C_{min}, t_{max}, $AUC_{(0\text{-}tau)}$, $t_{1/2}$ following last dose 2. Accumulation ratio (AR) for both C_{max} and AUC **PK-PD** Relationship between HMI-115 plasma concentration/exposure and pelvic pain score measured by NRS (cyclic = DYS, non-cyclic = NMPP+DYSP, and average)/side effects **Immunogenicity:** Anti-drug antibody (ADA)

4 Study Design

4.1 Overall Design

This is a Phase 2, multicenter, double-blind, placebo-controlled, randomized study to assess the safety and efficacy of HMI-115 subcutaneously administered monoclonal antibody versus placebo in pre-menopausal women with moderate to severe endometriosis-associated pain. The planned study regions include China, the United States of America (USA) and European countries.

The study will comprise of three periods (refer to Figure 1-1):

1. **Screening Period** of up to 75 days prior to first dose

    - Screening Visit 1
    - Screening Visit 2 (at least 35 days before V3 to ensure at least 5 weeks baseline pain score obtained before randomization)

2. **Treatment Period** (12 weeks). Subjects will be given subcutaneous (s.c.) injections Q2W in the study.

3. **Follow-up Period** of 12 weeks

Eligible subjects will be randomized into four arms: placebo, 60 mg, 120 mg, and 240 mg HMI-115 in a 1:1:1:1 ratio with 38 subjects/arm.

Blood samples will be collected to determine PK profile from Day 1 to Day 169. A full PK sampling strategy will be followed for a subgroup of 10 subjects per arm (refer to Table1-2). Sparse sampling will be obtained from the rest of the subjects (refer to Table1-3). Plasma concentrations of HMI-115 will be determined using a validated enzyme-linked immunosorbent assay (ELISA) method. PK parameters will be assessed as described in Section 9.4.9.

An e-Diary will be dispensed, and training will be provided to subjects at the Visit 2 on how to record endometriosis-associated pain, uterine bleeding, and rescue medication use for endometriosis-associated pain on a daily basis. Study-related examinations, laboratory assessments and pregnancy testing will be performed according to the SoA throughout the study (refer to Table 1-1).

*Note**:** Environmental sanitization procedures will be implemented in the study site and where study procedures are conducted. The study design and associated safety measures are deemed appropriate for conduct during COVID-19 pandemic*.

4.2 Scientific Rationale for Study Design

Evaluation of different doses of HMI-115 together with placebo will allow for further evaluation of efficacy and safety of the drug. A parallel design is preferable due to the long half-life of HMI-115, i.e., 6 doses over 12 weeks will be administered to reach steady state.

4.3 Justification for Dose

4.3.1 PK Modeling and Simulation of HMI-115

To date, a multi-center, randomized, double-blind, placebo controlled, first-in-human study to investigate the safety, tolerability, and pharmacokinetics of HMI-115 following single and

repeated subcutaneous administration to healthy postmenopausal women was completed in Germany.

In summary, escalating subcutaneous single doses of 0.75 mg - 240 mg of HMI-115 and subcutaneous multiple doses (up to three administrations) of 30 mg - 90 mg of HMI-115 given every other week (Q2W) were well tolerated in healthy postmenopausal women.

To predict the steady-state PK exposure of HMI-115 in humans at dosing regimens higher than 90 mg Q2W, modeling and simulations were conducted using a population PK model developed based on PK data from repeat doses (30 mg Q2W, 60 mg Q4W and 90 mg Q2W) FIH study in post-menopausal women.

The predicted C_{max}, C_{trough} and AUC after a single dose administration of 240 and 480 mg are shown in Table 4-1. Following a 240 mg Q2W dosing regimen. The average steady state C_{max}, and $AUC_{(0-\tau)}$ were predicted to be 36.6 mg/L and 11,008 mg·h/L, respectively. Following a 480 mg Q2W dosing regimen, the average steady state C_{max} and $AUC_{(0-\tau)}$ were predicted to be 74.3 mg/L and 22,377 mg·h/L, respectively (Table 4-2).

Table 4-1. Summary of Simulated PK Parameters (Geometric Mean [90%CI]) after a Single Dose Administration of HMI-115

Doses	AUC_{tau} (mg·h/L)	C_{max} (mg/L)	C_{trough} (mg/L)
240 mg	3475 [2099-5760]	12.4 [7.57-20.4]	9.76 [5.63-16.7]
480 mg	7015 [4259-11583]	25.0 [15.3-40.9]	19.9 [11.6-33.9]

Table 4-2. Summary of Simulated PK Parameters (Geometric Mean [90%CI]) at Steady-State for HMI-115

Doses	$AUC_{tau,ss}$ (mg·h/L)	$C_{max,ss}$ (mg/L)	$C_{trough,ss}$ (mg/L)
240 mg Q2W	11008 [5310-23073]	36.6 [18.5-73.8]	27.3 [12.0-61.4]
480 mg Q2W	22377 [10858-46682]	74.3 [37.7-149]	55.6 [24.7-124]

* Calculated for tau=2W for direct comparison; ss = steady state

4.3.2 Prediction of Efficacious Dosing Regimens of HMI-115

A significant reduction in interna endometriosis score (full response in all animals) was observed when animals were treated with the BAY 1158063 which is HMI-115 in the murine IgG2a format (closely related to HMI-115 with similar properties) at the dose of 30 mg/kg once weekly for 7 weeks (refer to IB). Exposure to the drug in mice was not measured in the study, however, the extrapolation of exposure based on the C_{trough} of 70mg/L observed after 65 mg/kg single dose treatment on mice, translates into a C_{trough} of 35 mg/L at 30mg/kg dosage. Corrected for species

differences in potency, which is 3.8 calculated from the IC50 between mice vs human (4.2nM/1.1nM) based on cellular proliferation assay performed on Ba/F3 cells transfected with human, mice and monkey PRLR, and assuming similar tissue distribution between mice and human, it is anticipated that a $C_{trough,ss}$ above 10 mg/L is needed in humans to achieve maximum effect (response in all subjects). Based on PK simulations, a dose of 240 mg Q2W would be needed for all subjects to reach $C_{trough,ss}$ at 12 mg/L.

Similarly, a partial reduction of the interna endometriosis score was observed in mice treated with 10 mg/kg weekly for seven weeks. Thus, the dose in human most likely to produce a similar exposure as that in mice treated with 10 mg/kg after correction by differences in drug potency, and assuming similar tissue distribution between mice and human, it is anticipated that minimum effective dose is 60 mg Q2W. Therefore, the doses of 60 mg Q2W as minimum effective dose and 240 mg Q2W as maximum effective are proposed.

4.3.3 Estimated Safety Margins for HMI-115

HMI-115 was well tolerated in 13-week repeat-dose toxicity studies in mice and Cynomolgus monkeys. No signs of systemic toxicity were observed after repeated once weekly s.c. administrations at doses up to 400 mg/kg (mice) and 100 mg/kg (monkeys) over a period of 13-week. Thus, the high dose was considered the No Observed Adverse Effect Level (NOAEL) in these studies. The exposure at the NOAEL the end of the treatment period was used to calculate the safety margins along with the estimated exposure at the anticipated human dose of 240 mg and 480 mg given Q2W.

Table 4-3. Safety Margins for HMI-115 after Subcutaneous Administration *Based on AUC* (mg×h/L)

Species/Sex	NOAEL (mg/kg/day)	Duration of Dosing	$AUC_{(0–168)}$ (mg·h/L)	Safety Margin (240 mg Q2W)[a]	Safety Margin (480Q2W)[b]
Mouse/Male	400	13 weeks	390000	35	17.4
Mouse/Female	400	13 weeks	150000	14	6.7
Monkey/Female	100	13 weeks	181000	16	8.1
[a,b] Estimated exposures at 240 mg Q2W ($AUC_{t,ss}$ of 11008 mg·h/L) or 480 mg Q2W ($AUC_{t,ss}$ of 22377 mg·h/L) were used to calculate margins					

Table 4-4. Safety Margins for HMI-115 after Subcutaneous Administration Based on C_{max} (mg/L)

Species/Sex	NOAEL (mg/kg/day)	Duration of Dosing	Cmax (mg/L)	Safety Margin (240 mg Q2W)[a]	Safety Margin (480Q2W)[b]
Mouse/Male	400	13 weeks	3160	86	43
Mouse/Female	400	13 weeks	2360	64	32
Monkey/Female	100	13 weeks	1540	42	21
[a,b] Estimated exposures at 240 mg Q2W (C_{max} of 36.597 mg/L) or 480 mg Q2W (C_{max} of 74.297mg/L) were used to calculate margins					

The predicted steady state HMI-115 exposures are well below the NOAEL values (C_{max}=1,540 mg/L and $AUC_{(0\text{-}168h)}$=181,000 mg·h/L) reported in a 13-week GLP toxicology study in the most sensitive studied species, the Cynomolgus monkey, suggesting that the repeated dose regimens (240/480 mg Q2W) are appropriate with sufficient safety coverage with respect to both $AUC_{(0\text{-}tau)}$ and C_{max} (Table 4-3 and Table 4-4).

Thus, the available nonclinical safety data are considered to provide adequate support for the proposed Phase 2 study in patients with endometriosis.

4.4 End of Study Definition

A subject is considered to have completed the study if she has completed all phases of the study including the last scheduled procedure (follow-up at Week 25 for safety and to cover 5 half-lives) as shown in the SoA.

The end of the study is defined as the date of the last visit of the last subject in the study or last scheduled procedure shown in the SoA for the last subject in the study globally.

5 Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

The study population will consist of subjects with moderate to severe endometriosis-associated pain. Subjects must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Pre-menopausal female subjects, between 18 and 49 years of age, inclusive, at the time of signing informed consent.
2. Subject must have a clinical diagnosis of endometriosis (laparoscopy or laparotomy) as documented by medical records within 10 years before screening.
3. Subject must have a Composite Pelvic Signs and Symptoms Score (CPSSS, refer to Section 8.11 and 10.9) total score of ≥ 6 at screening with a score of at least 2 for DYS and at least 2 for NMPP.
4. Subject must have reported at Baseline at least 2 days of "moderate" or "severe" pain for DYS and NMPP, with NRS score of at least 4 (where 0 represents absence of pain and 10 indicates unbearable pain, refer to Section 8.1.3 and 10.6).
5. Mammography or contrast-enhanced breast MRI performed within the last 12 months prior to randomization without clinically significant abnormal findings in subjects aged 40 and over only (subject with BI-RADS Classification 1 – 3 is eligible for randomization).
6. Subject must have at least two consecutive regular menstrual cycle (i.e. 21 to 35 days in duration) prior to Day 1.
7. Subject agrees to use required (nonhormonal) birth control methods during the entire length of participation in the study (refer to Section 10.4) and agrees to avoid pregnancy from signing the informed consent until 3 months after the last dose.
8. Subject must agree to use only those rescue analgesics (i.e. not prophylaxis) permitted by the protocol during the Screening, Treatment and Posttreatment follow-up Periods for her endometriosis-associated pain. (refer to Section 6.5.1).

9. In the Investigator's opinion, subject is able to understand the nature of the study and any risk involved in participation in this study and is willing to cooperate and comply with the protocol restrictions and requirements, including transvaginal ultrasound (TVU).
10. Subject agrees not to participate in another interventional study while participating in the present study.
11. Subject who is willing to limit alcohol consumption during the study to no more than approximately one alcoholic drink or equivalent [beer (354 mL/12 ounces), wine (118 mL/4 ounces), or distilled spirits (29.5 mL/1 ounce)] per day.

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply

1. Subject with confirmed SARS-CoV-2 infection, within 2 weeks prior to Screening or randomization.
2. Subject who had severe course of COVID-19 (extracorporeal membrane oxygenation [ECMO], mechanically ventilated).
3. Subject is pregnant or breastfeeding or is planning a pregnancy during the study period or is less than 6 months post-partum or 3 months post-abortion at the time of entry into the Screening Period or pregnancy before randomization.
4. Subject has an intra-uterine device (IUD) (refer to Section 10.5).
5. Subject has chronic pelvic pain that is not caused by endometriosis (e.g., interstitial cystitis, irritable bowel syndrome) or has any other chronic pain syndrome (e.g., fibromyalgia, chronic back pain, myofascial pain syndrome, chronic headaches) that requires chronic analgesic or other chronic therapy, which would interfere with the assessment of endometriosis-related pain.
6. Subject has clinically significant gynecologic conditions other than endometriosis, including but not limited to:
   a. Ovarian cyst>5 cm (except confirmed endometrioma) that persists on repeat TVU;
   b. Single fibroid ≥ 4 cm or multiple (> 4) fibroids that measure ≥2 cm or symptomatic submucosal fibroid of any size on screening TVU;
   c. Any ovarian tumors or pelvic masses of unclear etiology requiring further diagnostic procedures;
   d. Acute or chronic endometritis
7. Subject has a current history of undiagnosed abnormal genital bleeding.

8. Subject has history of hysterectomy and/or bilateral oophorectomy.
9. Subject has had surgery for endometriosis within the 4 weeks prior to entry into the Screening Period.
10. Subject plans to schedule elective surgery during the study execution.
11. Subject has known any history of anterior pituitary, posterior pituitary or hypothalamic dysfunction, including but not limited to prolactinomas, hypogonadism, growth hormone deficiency.
12. Subject has a current history of hyperthyroidism or uncontrolled hypothyroidism.
13. Subjects with past or present pituitary tumor growth as confirmed by a sellar magnetic resonance imaging (MRI) with contrast at screening period or has contraindications to contrast used in MRI.
14. Subjects with immunocompromised status (e.g, congenital immune deficiency syndrome, or currently under immunosuppressive therapy, etc.).
15. Subjects with a personal or family history of Multiple Endocrine Neoplasia syndrome type 1 (MEN1).
16. Subject has previous history of a severe, life-threatening or other significant sensitivity to any opioids or non-steroidal anti-inflammatory drugs (NSAIDS）or any contraindication to their use such as gastrointestinal ulcer or bleeding.
17. Subject with known hypersensitivity to any of the IMP ingredients.
18. Subject has a positive result on the screening urine drug screen and/or per the investigator's discretion, has had a history of drug or alcohol abuse or dependence within the last year.
19. Subject has, in the Investigator's opinion, uncontrolled hypertension (systolic blood pressure [SBP] > 159 mmHg, diastolic blood pressure [DBP] > 99 mmHg) at Screening Period.
20. Subject has an estimated glomerular filtration rate (eGFR) of < 60mL/min/1.73 m^2 (using the Chronic Kidney Disease Epidemiology Collaboration [CKD EPI] formula) at Screening Period.
21. Subject is currently participating in or has participated in an interventional clinical study with an investigational compound or device within 90 days prior to the start of Screening Period or 5 half-lives, whichever is longer. If a subject has participated in an investigational study with hormonal treatment, the minimal washout period applies as given in Section 10.5 also need to refer.

22. Subject has used medications such as hormones, analgesics, medications associated with bone loss, products that affect PRL levels, etc. within specific time window before Screening (refer to Section 10.5).

23. Subject with current or past use of any of the following drugs to treat osteoporosis:

    a. Bisphosphonates, Denosumab, Teriparatide, Abaloparatide, Romosozumab and Calcitonin.
    b. Strontium or Fluoride (other than for dental indication).
    c. Selective estrogen receptor modulators: Raloxifene, Bazedoxifene, Lasofoxifene, Clomifene, Tamoxifen, etc

24. Subject has clinically significantly abnormal laboratory tests at Screening Period, including:

    a. Alanine transaminase (ALT/SGPT), or aspartate aminotransferase (AST/SGOT) ≥200% of the upper limit of normal, or total bilirubin (unless known diagnosis of Gilbert's syndrome) ≥ 150% of the upper limit of normal range.
    b. Hemoglobin < 10 g/dL, Neutrophil count < 1500 mm^3, Platelet count < $100 \times 10^3/mm^3$.

25. Subject has cervical cytology collected during the Screening Period shows evidence of malignancy or pre-malignant changes.

26. Subject has clinically significant abnormal ECG, or ECG with QTcF > 450 msec at Screening Period.

27. Subject has a positive Screening test result for hepatitis A virus immunoglobulin M (HAV – IgM), hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), detected HCV RNA (for positive or equivocal anti-HCV), or positive human immunodeficiency virus (HIV) or HIV antibody (HIV Ab). The HIV/HIV Ab results will be kept confidential by the study sites.

28. Subject has a history of active malignancy (with or without systemic chemotherapy), except treated basal cell carcinoma of the skin.

29. Subject is using any systemic corticosteroids for over 14 days within 3 months prior to Screening or is likely to require treatment with systemic corticosteroids during the course of the study. Over-the-counter and prescription topical, inhaled or intranasal corticosteroids are allowed.

30. Subject has a medical history of confirmed psychiatric disorder (e.g., major depression, post-traumatic stress disorder, schizophrenia, bipolar disorder) or has a history of suicide attempt or epilepsy, for whom it would not be recommended to stop concurrent medication therapy or may require medication therapy during study participation (refer to Section 6.5.2 and 10.5 for prohibited medication and washout period).

31. Subject has any of the following conditions within 6 months prior to Screening:
    a. Myocardial infarction, stroke, unstable angina or transient ischemic attack.
    b. Classified as being in New York Heart Association Class III or IV.
32. Subject has a history of osteoporosis or other metabolic bone disease, or including any one or more of the following:
    a. Low bone mass (Z-score ⩽ -1.5 on screening DXA scan [lumbar spine, femoral neck or total hip BMD]) OR
    b. Body weight greater than 300 pounds or 136 kilograms (due to limits of DXA scanners) or any condition that would interfere with obtaining adequate DXA measurements (e.g., history of spinal surgery, severe scoliosis, hardware or artifact overlying the region of interest, including umbilical ring with refusal to remove)
    c. History of fragility fracture OR
    d. History or presence of an unstable condition that is associated with a decrease in BMD (e.g., uncontrolled hyperparathyroidism, anorexia nervosa)
33. Any other conditions in the investigator's opinion that prevent the subject from participating.
34. Subject works in the investigational site or has an immediate family member (e.g. spouse, parent/legal guardian, sibling or child) who works in the investigational site or is a staff of the Sponsor directly involved with this study.

Procedures that are allowed to be repeated for screening are listed in section 10.10

5.3 Lifestyle Considerations

For the duration of the study, subjects must agree to adhere to local requirements for reduction of the public SARS-CoV-2 exposure. This may include, but is not limited to:

- Practice "social distancing" or similar as defined by their local health authorities and refrain from joining large gatherings of people
- Wear a face mask in enclosed public spaces and/or when using public transportation if required by local regulations
- Wash their hands with soap for at least 20 seconds regularly throughout the day (e.g., every time after using the washroom) and immediately after returning from a trip outside their home
- Make every effort to refrain from touching their face unnecessarily

- While visiting the study site, physical distancing and person-to-person contact restrictions will be applied and explained to subjects. Where physical distancing is not possible subjects will be asked to use surgical face masks, gloves and/or face shields if deemed appropriate by the Investigator and site staff and guided by local requirements.

5.3.1 Prolactin Sampling

Prior to PRL sampling, the subject must be examined and instructed to avoid PRL influencing factors such as emotional/physical stress, high-protein meals, all forms of chest and breast stimulation, including sexual activity and impact exercises such as running/jogging (these factors should be avoided on the morning prior to blood sampling), or any medication influencing PRL levels (refer to Section 6.5.2).

5.3.2 Activity

Subjects will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watching television, reading).

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to the IMP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure (e.g., eligibility requirements failed), and any serious adverse events (SAEs).

Individuals who originally do not meet the criteria for participation in this study (screen failure) may be rescreened once when Investigator considers the patient to be eligible to be enrolled. Rescreened subjects should be assigned a different subject ID and will be considered a new subject.

5.5 Screening and Enrollment Log and Subject Identification Numbers

The subject's enrollment will be recorded in the Screening and Enrollment Log. Upon enrollment, each subject will receive a unique subject identification number. A rescreened subject will be given a new identification number.

6 Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol. In this regard, study interventions in this study include Investigational Medicinal Products (IMPs)（HMI-115, placebo） and Non-Investigational Medicinal Products (NIMP) (rescue medications).

6.1 Study Intervention(s) Administered

The following study interventions will be administered to the subject:

Table 6-1. IMPs Administered

Arm Name:	**Placebo**	**HMI-115 60 mg**	**HMI-115 120 mg**	**HMI-115 240 mg**
Intervention Name:	Placebo	HMI-115	HMI-115	HMI-115
Type:	Drug	Drug	Drug	Drug
Dosage Formulation:	Lyophilized form	Lyophilized form	Lyophilized form	Lyophilized form
Unit Dose Strength(s):	NA	60mg/vial	60mg/vial	60mg/vial
Dosage Levels:	Placebo Q2W	60 mg Q2W; 12 weeks (6 treatment cycles)	120 mg Q2W; 12 weeks (6 treatment cycles)	240 mg Q2W 12 weeks (6 treatment cycles)
Route of Administration:	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous
Use:	Placebo	Experimental	Experimental	Experimental
Sourcing:	Provided centrally by the Sponsor			
Packaging and Labeling:	IMP will be provided in vials. Kits containing the vials will be labeled as required per country requirement.			

Table 6-2. IMP(s) and Dosing Schedules

Arm Name:	**Placebo Q2W**	**HMI-115 60 mg Q2W**	**HMI-115 120 mg Q2W**	**HMI-115 240 mg Q2W**
Dosing schedules	Placebo: 4mL	HMI-115 60mg/mL: 1 mL Placebo: 3 mL	HMI-115 60mg/mL: 2 mL Placebo: 2 mL	HMI-115 60mg/mL: 4 mL

In general, all subcutaneous injections were in the upper or lower abdomen around the belly button, but at least 1 cm away from the belly button itself.

Repeated injections in the same spot can cause scarring and hardening of subcutaneous tissue, and therefore should have been avoided. Each injection should have been at least 2.5 cm apart.

Different injection sites should be used between visits to in case the occurrence or worsening of injection site reactions.

IMP administration should be performed after blood sampling and vital signs examination during each visit.

Note: For subjects who fail to visit the study site on schedule, subject will be requested to return to site and complete the study visit as soon as possible. If the rescheduled visit is within one week (i.e., < 7 days) of the next scheduled visit, the schedule of all the subsequent visits will be adjusted based on this visit date and dosing will follow the Q2W interval.

6.2 Preparation, Handling, Storage, and Accountability

The lyophilized Drug Product must be stored at 2-8°C. Requirements for aseptic operation should be followed during IMP preparation. Unless administered immediately, for microbiologic consideration, the reconstituted solution should be stored at 2-8°C or room temperature, and administered within 4 hours.

If the solution has been frozen, it must no longer be used for application and should therefore be discarded.

The Investigator or designee must maintain a log to confirm appropriate temperature conditions have been maintained during transit for all IMPs received and any discrepancies are reported and resolved before use of the IMP.

Only subjects enrolled in the study may receive the IMP and only authorized site staff may supply or administer IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (e.g., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused IMPs are provided in the Study Reference Manual or other specified location.

6.3 Measures to Minimize Bias: Randomization and Blinding

All subjects will be centrally randomized using an Interactive Response Technology (IRT). The randomization will be stratified with two stratification factors 1) region and 2) participation in the intensive PK sampling subset. Each subject will be assigned a unique number (randomization number) that encodes the subject's assignment to different arms of the study. Details of the procedure are described in the IRT Manual provided to all sites. IMP will be administered/dispensed at the study visits summarized in Section 6.

6.4 Study Intervention Compliance

The subjects will receive the study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the study site will be recorded in the source documents and recorded in the electronic case report form (eCRF). The IMP to be used and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the IMP.

When subjects self-administer rescue medications at home, the type and dosage of rescue medication will be assessed at each visit. Compliance will be assessed by direct questioning (for e-Diaries) and counting returned rescue medication during the site visits and documented in the source documents and eCRF.

6.5 Concomitant Therapy

Any medication or vaccine (including vaccines for COVID-19, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

No pain medications other than the prescribed pain medication as rescue medication can be taken during the study duration. Further details on prohibited medications have been presented in section 6.5.2.

6.5.1 Rescue Medications

Protocol specific analgesic rescue medication for endometriosis-associated pain will include four equivalent NSAID choices and three equivalent opioid choices. The protocol-allowed analgesic rescue medications for endometriosis-associated pain are presented in Table 6−3. Investigators will prescribe a specific analgesic rescue medication for subjects at the time of Visit 2, taking into consideration the subject's preference and/or historical use of analgesics and the investigator's clinical judgement (based on the approved options).

Investigators are not to suggest or advise subjects on any modifications to their rescue medication regimen. Subjects will be instructed to contact the site if a change in their rescue analgesic medication is needed, such that appropriate adjustments can be considered. Investigators may then prescribe a different analgesic rescue medication (from each medication class if necessary) for the subject. Investigators should not prescribe more than one analgesic rescue medication from the same medication class at one time. The dosage outlined in Table 6-3 could be utilized, but all prescribed use of rescue analgesic medication should be according to appropriate clinical practice standards and the investigator's clinical judgment.

It is the investigator’s discretion whether to withdraw a subject due to an analgesic issue.

Prophylactic use of protocol-specific rescue analgesic medications is not allowed. Use of any other analgesic medications for endometriosis-associated pain, including prophylactically, is not allowed from Visit 2 through the Follow-up Period.

Daily use of rescue analgesic medications taken for endometriosis-associated pain will be recorded by the subject in the e-Diary from Visit 2 through the Follow-up period including date of rescue medication use as well as the name, dosage and total number of the rescue medication within a 24-hour period. Detailed information on the rescue medication that will be sourced and provided to the subject can be found in the site operation manual. In addition, any pain medication taken for pain other than for rescue (such as treatment for toothache etc.) will be recorded in eCRF, not in the e-Diary.

Use of a prohibited medication for treatment of endometriosis-associated pain will be documented in the eCRF. If a subject continues to take analgesic(s) other than the protocol-

specified rescue analgesics for endometriosis-associated pain, her continued participation in the study will be evaluated by the investigator and the Medical Monitor.

If there are any questions regarding rescue therapy, please contact your Medical Monitor.

Table 6-3. Permitted Rescue Medication for Endometriosis-Associated Pain

Medication class	Medication Name	Dosing Strength*	Country
NSAIDS	Ibuprofen	200 mg	All
NSAIDS	Naproxen#	200 mg	All
NSAIDS	Diclofenac^	25 mg	All
NSAIDS	Celecoxib	50 mg	All
Opioid Analgesics	Hydrocodone +acetaminophen	5 mg Hydrocodone+ 300 or 325 mg acetaminophen	All
Opioid Analgesics	Codeine phosphate +acetaminophen$	30 mg codeine+300 mg acetaminophen$	All
Opioid Analgesics	Tramadol + acetaminophen	37.5mg tramadol + 325mg acetaminophen	All

* Use of these rescue analgesic medications should be according to appropriate clinical practice standards and Investigator's clinical judgment.
# Naproxen 200 mg is equivalent to naproxen sodium 220 mg.
^ Diclofenac Immediate-Release product is preferred.
$ Combination with or without caffeine is permitted.

6.5.2 Prohibited Medications

The following medications are prohibited for the entire study duration.

Table 6-4. Prohibited Medications

Prohibited Medications
Hormonal/Anti-Hormonal Therapy
GnRH agonist
GnRH antagonists
Danazol
Medroxyprogesterone Acetate
Contraceptives (e.g. oral, patch, injectable and implanted)
Levonorgestrel (except emergency contraception, i.e., levonorgestrel 1.5 mg)
Other Progestins (e.g. oral, injectable, patch, vaginal, IUDs, implanted)
Mifepristone
Testosterone preparations

Prohibited Medications	
Aromatase Inhibitors Menotropins and human chorionic gonadotropin (hCG)	
Medications that affect PRL level	
Antiepileptics and anticonvulsants	Diazepam, Phenytoin Sodium, Phenobarbital, etc.
Antipsychotics and antidepressants	Sulpiride, Risperidone, Haloperidol, Clomipramine, Phenothiazines, Nomifensine, etc.
Injection use of Histamine H1/H2 receptor antagonists	Promethazine, Famotidine. etc.
Other medications that affect PRL level	Bromocriptine, Cabergoline, Lergotrile, Lisuride, Metergoline, Quinagolide, Terguride, Isoniazide, Domperidone, Metoclopramide, Reserpine, Methyldopa, etc.
Analgesics	
Any analgesic medications other than protocol specified ones for endometriosis-associated pain, including prophylactically	
Osteoporosis drugs	
Bisphosphonates, Denosumab, Teriparatide, Abaloparatide, Romosozumab and Calcitonin. Strontium or Fluoride (other than for dental indication). Selective estrogen receptor modulators: Raloxifene, Bazedoxifene, Lasofoxifene, etc.; Clomifene, Tamoxifen,etc.	
Others	
Growth hormone replacement Cannabinoids Systemic corticosteroids (oral or injectable) Misoprostol Herbal remedies containing Hypericum perforatum (e.g. Kava kava and St. John's wort) Anti-tumor necrosis factor (TNF)/anti-nerve growth factor (NGF) Medications that are covered by **urine drug screen** (if applicable)	

If in the Investigator's opinion, subject needs to take prohibited medication(s) continuously for any reason, her continued participation in the study will be evaluated by the investigator and the Medical Monitor.

If a hormonal emergency contraception is used, the use of the drug and any associated menstrual cycle irregularity after the use should be documented.

If there are medications not listed in the table above that need further clarification, consult the Hope Medicine Medical Monitor for suggestions.

6.6 Dose Modification

Not applicable.

6.7 Intervention After the End of the Study

There will be no study intervention after the end of the study. Subjects could follow the routine medical practice.

7 Discontinuation of IMP and Subject Withdrawal

7.1 Discontinuation of IMP

It may be necessary for a subject to permanently discontinue (definitive discontinuation) the IMP. If the IMP is definitively discontinued, the subject will remain in the study until Visit 10 to be evaluated for safety and efficacy of the IMP. Please refer to Section 10.4 and 8.4.5 for details on contraceptive guidance and collection of pregnancy information.

The Investigator or Medical Monitor (and, if needed, with DMC review) may temporarily hold or stop the dosing of IMP to a subject at any time during the study. For subjects that discontinue IMP for reasons related to safety, unblinding of the treatment assigned to the subject may be carried out if deemed necessary by the Sponsor to assess any potential safety signal or by the Investigator to provide adequate medical care to the subject. All details of reasons, therapies that may have been subsequently started should be well documented and reviewed.

Examples of conditions or symptoms that may warrant holding or stopping IMP at the Investigator's and/or Medical Monitor's discretion include:

- Occurrence of a severe or serious AE assessed as related to IMP
- Repeating premature ventricular contractions (PVC) confirmed by additional ECG examination at least 30 minutes apart, or QTcF interval >500 ms, or increase in QTcF interval >60 ms compared to baseline in absence of possible causes other than the IMP
- Significant decrease of neutrophils count < 1500 mm^3 confirmed by repeat measurement

- Pregnancy
- Intolerance of the IMP authorized under this protocol
- If in the Investigator's opinion, continuation with the administration of the IMP would be detrimental to the subject's well-being

Investigator must notify the Sponsor within one calendar day of being aware of an event that may warrant holding or stopping the IMP. If the IMP is held due to safety concerns, approval by the Medical Monitor is required prior to resumption of IMP. If the subject meets the holding or stopping conditions again after resumption (re-challenge), the IMP will be permanently discontinued.

Unless informed consent is withdrawn, subjects who permanently discontinue IMP during the treatment period should attend all subsequent visits up to Visit 10 and complete all procedures (except IMP administration related) as outlined in the SoA.

7.2 Subject Withdrawal from the Study

The subject may withdraw or may be withdrawn from the study:

- If they decide to do so, at any time and irrespective of the reason
- At the specific request of the Sponsor

Subject discontinuation from IMP or withdrawal from the study should be avoided as much as possible. Every attempt should be made to restart IMP if medically appropriate and approved by Medical Monitor, irrespective of the duration of holding IMP.

In the event of withdrawn from the study during the treatment period, if possible, an early discontinuation visit (procedures same as Visit 9) needs to be performed as soon as possible and an on-site follow-up visit (procedures same as Visit 10) after 12 weeks from the last dose should be conducted. If the subject is unwilling to attend the on-site follow-up visit, a follow-up phone call should be attempted if the subject agrees, to collect safety information (monitoring AE, pregnancy status, concomitant medications) (refer to Section 1.3).

In the event of withdrawn from the study during the follow-up period, if possible, an on-site follow-up visit (procedures same as Visit 10) is recommended to complete as soon as possible followed by a phone call follow-up at 12 weeks from the last dose to collect safety information (monitoring AE, pregnancy status, concomitant medications). If the subject is unwilling to attend an on-site

follow-up visit, a phone call follow-up at 12 weeks from the last dose should be attempted if the subject agrees (refer to Section 1.3).

If the subject withdraws informed consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

Note: For subjects discontinued from IMP or withdrawn from study, no additional PK and ADA sampling except EOT and EOS visits (if possible) is required after IMP discontinuation.

Handling of subjects with suspected COVID-19 infection:

If a subject develops fever or symptoms suspected of being a result of COVID-19 during the study, they will be instructed to follow-up with their regular healthcare provider or follow the instructions for suspected COVID-19 cases per their local health authority.

A subject may be withdrawn by the Investigator based on discussion with the Sponsor and Medical Monitor under the following circumstance:

- any confirmed COVID-19 case that warrants withdrawal in the judgment of the Investigator or Sponsor to protect the safety of the subject, other study subjects or study site staff.

7.3 Study Pauses for Safety Reasons

In order to monitor and protect the safety of study subjects, to ensure early insight into any safety signal, and for early elimination of any potential safety hazard for an individual subject or a full cohort/entire study population, the Medical Monitor will review all AEs from the entries in the eCRF on an ongoing basis and SAE reports as received. An independent DMC will be established and will review all study data pertaining to subjects' safety on a regular basis to adjudicate the overall safety of the subjects in this study. In addition, the DMC will be notified, and a meeting may be called for each case of IMP discontinuation due to an IMP related safety reason.

Study will be paused pending prompt review by DMC if 2 or more subjects experience similar SAE or severe AE assessed as related to IMP, or discontinue IMP for safety reasons assessed as related to IMP.

Study will be paused if any of the following assessed as related to IMP occurs, pending prompt review of the case(s) by the DMC: death, suicide attempt, serious changes in behavior (such as

psychosis or the development of impulse control disorders or addictive behavior), cardiac arrhythmia or AEs pertaining to the pituitary gland.

7.4 Loss of Subjects to Follow-Up

A subject will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible (and within the visit window, where one is defined) and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases in which the subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

  Should the subject continue to be unreachable, she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Table 1-1). Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening and enrollment log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (e.g., mammography) and obtained before signing of the informed consent form (ICF) may be utilized for Screening

purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Informed Consent

Informed consent must be documented according to Section 10.1.3.

Eligibility Criteria

All inclusion and exclusion criteria will be reviewed by the Investigator or designee to ensure that the subject qualifies for the study.

Subject Identification Card

All subjects will be given a subject identification card identifying them as subjects in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The Investigator or qualified designee will provide the subject with a subject identification card immediately after the subject provides written informed consent. At the time of randomization, site personnel will add the randomization number to the subject identification card.

The subject identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about IMP in emergency situations where the Investigator is not available.

Demographic information

The following demographic information will be recorded:

- Age
- Ethnic origin
- Race
- Height in cm
- Body weight (in kg)

Medical history

A medical history will be obtained by the Investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed prior to signing informed consent that the Investigator considers to be clinically significant. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

Prior and concomitant medications review

The Investigator or qualified designee will review prior medication use and record prior medications taken by the subject within 1 month prior to Screening. For medications related to the inclusion/exclusion criteria with specific washout period, refer to Section 10.5 for the time requirement.

The Investigator or qualified designee will record medication, if any, taken by the subject during the study through the last visit. Concomitant medications will be recorded until last study visit.

All reasonable measures will be taken to decrease potential transmission of COVID-19; for example, study staff and physicians will wear surgical masks and gloves and/or face shields while meeting with subjects and will wash their hands per the Center for Disease Control (CDC)/World Health Organization (WHO)/regional health authority guidelines before, between, and after meeting each subject.

8.1 Efficacy Assessments

8.1.1 Electronic-Diary (e-Diary)

All subjects will be administered an e-Diary after adequate training at Visit 2. Subjects are required to record uterine bleeding and endometriosis-associated pain every day at around the same time for the entire duration of the study. The use of rescue medications for endometriosis-associated pain will also be recorded. Compliance to e-Diary filling will be assessed as shown in the SoA (refer to Section 1.3). Subjects need to return the e-diary devices after the completion of study participation or after withdrawal from the study.

8.1.2 Evaluation of the need for Rescue Medication

Subjects will be supplied rescue pain medication (as listed in Table 6-3) that should be used only for endometriosis-associated pain throughout the study duration. Assessment will be based on the average number of rescue medication consumed by the subject and the percentage of days the subject took rescue medication.

8.1.3 Numeric Rating Scale (NRS) for Pain

NRS pain scale will be used to measure DYS from Baseline to Week 12 and Baseline to Week 24 with Pain Scale ranging from 0 (no pain) to 10 (severe pain). Subjects will assess in the e-Diary their endometriosis-associated pain during the past 24 hours (last calendar day). NMPP and DYSP will be also measured using the NRS pain scale from Baseline to Week 12, and Week 24.

Refer to Section 10.6 for the template.

8.1.4 Endometriosis Daily Impact Pain Scale

Endometriosis Daily Impact Pain Scale will be used to record the mean change every month from Baseline to Week 12 and 24 with the Pain scale ranging from 0 (no pain) to 3 (severe pain).

Based on the subject's response to the question "Did you have your period in the last 24 hours (last calendar day)?" in the daily e-Diary, the subject will be asked to assess either their dysmenorrhea or non- menstrual pelvic pain as follows:

Dysmenorrhea (DYS)

Subjects will be asked to assess their DYS and its impact on their daily activities. Subjects will be prompted to "Choose the item that best describes your pain during the last 24 hours (last calendar day) when you had your period."

0	None	No discomfort
1	Mild	Mild discomfort but I was easily able to do the things I usually do
2	Moderate	Moderate discomfort or pain. I had some difficulty doing the things I usually do
3	Severe	Severe pain. I had great difficulty doing the things I usually do

Non-Menstrual Pelvic Pain (NMPP)

Subjects will be asked to assess their NMPP and its impact on their daily activities. Subjects will be prompted to "Choose the item that best describes your pain during the last 24 hours (last calendar day) without your period."

0	None	No discomfort

1	Mild	Mild discomfort but I was easily able to do the things I usually do
2	Moderate	Moderate discomfort or pain. I had some difficulty doing the things I usually do
3	Severe	Severe pain. I had great difficulty doing the things I usually do

Dyspareunia (DYSP)

Subjects will be asked to assess their dyspareunia (described as 'pain during sexual intercourse'). Subjects will be prompted to "Choose the item that best describes your pain during sexual intercourse during the last 24 hours (last calendar day)."

	Not applicable	I was not sexually active for reasons other than my endometriosis or did not have sexually intercourse
0	None	No discomfort during sexual intercourse
1	Mild	I was able to tolerate the discomfort during sexual intercourse
2	Moderate	Intercourse was interrupted due to pain
3	Severe	I avoided sexual intercourse because of pain

8.1.5 Uterine Bleeding

Subjects will be prompted to indicate if they had "Did you have any uterine bleeding in the last 24 hours (last calendar day)?" Subject will then document the intensity of the bleeding as follows:

0	None	
1	Spotting	A light amount of bleeding noted, no protection or panty shield only
2	Light	1 to 2 regular tampons or pads required in 24 hours
3	Medium	3 to 4 regular tampons or pads required in 24 hours
4	Heavy	More than 4 tampons or pads required in 24 hours

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of General appearance, HEENT (head, eyes, ears, nose, throat), Neck (including thyroid), Lung/pulmonary, Chest (including breast), Cardiovascular, Abdomen, Back, Neurological, Extremities, Skin and Lymph nodes, and will be performed at Visit 1, Visit 9 and Visit 10. Height (cm) and weight (kg) will also be measured and recorded at specified period shown in the SoA (refer to Section 1.3).

A brief physical examination will include, at a minimum, assessments of General appearance, HEENT (including extra-ocular movements), Neck, Lung/pulmonary, Breast, Cardiovascular, Abdomen, Extremities and Skin, and will be performed at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, and Visit 8. Additional physical examination may be necessary based upon the subjects' complaints.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

Vital signs will be assessed from Screening Period to EOT period and during the follow-up visit. Tympanic body temperature, pulse rate, respiratory rate, and blood pressure will be assessed. Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest (e.g. in a sitting position) for the subject in a quiet setting without distractions (e.g., television, cell phones).

8.2.3 Pelvic examination

The pelvic examination should specifically document presence or absence of uterine or adnexal induration and/or tenderness, with description of tenderness (location, intensity, e.g., mild, moderate or severe) if present. The results of pelvic examination will be used for CPSSS.

8.2.4 Electrocardiograms

12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS and QT. QT interval will be corrected for heart rate using Fridericia's correction formula (QTcF) and Bazett's correction formula (QTcB) respectively.

8.2.5 Clinical Safety Laboratory Assessments

Refer to Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency. Blood draw will not exceed 500 mL during the entire study period.

The Investigator must review the laboratory report, document this review, and record any clinically significant abnormal changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significant abnormal during participation in the study or within 14 days after the last dose of IMP should be repeated until the values return to normal or Baseline, or are no longer considered clinically significant by the Investigator or Medical Monitor, or subject lost to follow-up or death.

- If such values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, where possible, and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from laboratory assessments not specified in the protocol and performed at the institution's local laboratory result in the need for a change in subject management or are considered clinically significant by the Investigator (e.g., are considered to be an SAE or an AE or require dose discontinuation), then the results must be recorded in source document.

8.2.6 Transvaginal Ultrasound (TVU) Assessments

Assessments for TVU include, but are not limited to, the following:

- Endometrial thickness (double layer, mm)
- Other endometrial findings such as heterogeneity or other abnormality
- Presence, size and appearance of ovarian cysts or masses
- Presence, location and size of uterine fibroids
- Endometriomas

The Screening TVU may be repeated per protocol (e.g., ovarian cyst criteria) or as clinically appropriate. An unscheduled (elective) TVU may also be performed as clinically indicated for subject evaluation during the course of the study.

8.2.7 Dual Energy X-ray Absorptiometry （DXA）

DXA results of the lumbar spine, total hip, and femoral neck will be obtained at screening period and Visit 9. A central bone density vendor will be used to conduct blinded reads of DXA scans and manages the longitudinal quality control of DXA scanners at each imaging center. The data from these analyses will be electronically transferred from imaging center to the study database. Subject treatment management will be made based on the central review.

For individual subject, the degree of bone loss that requires a follow-up DXA scan(s) as follows:

a) Obtain a 6-month post-treatment follow-up DXA scan for subjects with change from pre-treatment baseline of ≤ -2.0% in the lumbar spine or ≤ - 2.5% total hip, or Z-score ≤ -2.0 (i.e., below the expected range for age) at any anatomic site (lumbar spine, total hip, or femoral neck).

b) If the subject does not meet the criteria for adequate recovery on her DXA scan at post-treatment month 6, refer to a bone specialist (Define adequate recovery as change from pre-treatment baseline of > -1.5% at the lumbar spine and > -2.0% at the total hip).

c) Refer to a bone specialist those subjects with Z-score ≤ -2.0 at any anatomic site at post-treatment month 6 (or on their final DXA scan if they do not follow-up as instructed).

The window period for EOT visit and post-treatment month 6 DXA scan is ±14 days.

Subjects who prematurely discontinue IMP treatment prior to week 11 will not have a DXA at the EOT visit or in the Post-treatment Follow-up Period. Subjects who become pregnant during the study will not have protocol required DXA scans.

8.3 Exploratory Assessments

8.3.1 Patient Global Impression of Change (PGIC) Score

Subjects will score the PGIC as shown in the SoA (refer to Table 1-1). The PGIC questionnaire is a self-reported 7-point scale rating a subject's overall impression of change in their endometriosis-associated pain since start of IMP, where 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = not changed, 5 = minimally worse, 6 = much worse, 7 = very much worse.

Refer to Section 10.7 for the template.

8.3.2 Endometriosis Health Profile-5 (EHP-5)[13]

The EHP-5 is a HRQoL scoring that has a core questionnaire and modular questionnaire with a 4-point rating scale for each item (0 = never, 1=rarely, 2=sometimes, 3=often, 4 = always). Anything that is not applicable to the subject in the questionnaire will be marked not relevant.

Refer to Section 10.8 for the template.

8.4 Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.3.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of ICF until the end of study participation at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Section 10.3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obliged to actively seek AEs or SAEs after the end of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to IMP or study participation, the Investigator must promptly notify the Sponsor.

8.4.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3) or death. Further information on follow-up procedures is given in Section 10.3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours, refer to Section 10.3) by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of subjects and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB) or Independent Ethic Committee (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy

All subjects should follow contraceptive guidance strictly as detailed in Section 10.4. However, in the event of pregnancy after start of study visit with relevant consent obtained:

- Details of all pregnancies in subjects will be collected from the signing of ICF until the end of study participation.
- If a pregnancy is reported, the Investigator should inform the Sponsor (or Sponsor designated agent) within 24 hours of learning of the pregnancy and complete the pregnancy report forms within 30 days.
- Investigator will collect pregnancy information on any subject, who becomes pregnant while participating in this study. Subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and neonate for one month after delivery, which will be forwarded to the Sponsor. For live infant births, information on the health of the infant will be collected 6 to 12 months after delivery.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- IMP should be discontinued permanently when pregnancy is identified.

Pregnancy alone is not regarded as an AE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs.

Elective abortions without complications should not be handled as AEs, unless the abortion was required for treatment of a specific AE. Hospitalization for normal delivery of a healthy newborn should not be considered a SAE.

Any SAE that occurs during pregnancy (including SAEs occurring after last administration of IMP) must be recorded on the SAE report form (e.g., maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the IMP by the Investigator, will be reported to the Sponsor. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

8.5 Treatment of Overdose

This study is a dose finding study and thus no data is available for treatment of overdose.

8.6 Pharmacokinetics

Plasma samples will be collected for measurement of plasma concentrations of HMI-115 at time points specified in the SoA (refer to Table1-2, and Table1-3). The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring. Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for analyses of HMI-115 plasma concentration may also be used to evaluate safety or efficacy aspects that address concerns arising during or after the study.

Subject confidentiality will be maintained. At visits during which samples for the determination of plasma concentration of HMI-115 will be taken, 1 blood draw of sufficient volume can be used.

Plasma samples collected for pharmacokinetics analysis will be retained for up to 5 years following study finalization for possible further characterization of pharmacokinetic profile of HMI-115 at a specialized laboratory.

Drug concentration information that may unblind the study will not be reported to study sites or blinded personnel until the study has been unblinded.

8.7 Pharmacodynamics

Not applicable.

8.8 Genetics

Pharmacogenomics will not be evaluated in this study.

8.9 Biomarkers

The following biomarkers will be evaluated: Prolactin and CA-125.

8.10 Immunogenicity Assessments

To assess the overall immunogenicity potential of HMI-115, subject's blood will be tested for anti-drug antibody (ADA) production: ADA (positive/negative and titer) and neutralizing antibodies (NAB) (positive/negative and titer only in subjects with ADA positive result). The time points for ADA determinations in blood are provided in SoA with one additional sampling point at week 17. All samples for ADA should be collected together with the corresponding PK sample.

Serum samples collected for immunogenicity assessments will be retained for up to 5 years following study finalization for possible further characterization of a potential ADA response at a specialized laboratory.

8.11 Composite Pelvic Signs and Symptoms Score (CPSSS)

The CPSSS is a rating instrument used to assess signs and symptoms of endometriosis. It consists of two sections completed by two different individuals. The first section (Section 1) is completed based on the subject's responses regarding DYS, DYSP, and NMPP. The first section should not be completed by the subject. This section should also not be completed by the individual who is completing the second section of the CPSSS. The second section (Section 2) is completed by the investigator based on findings associated with a pelvic examination (i.e., pelvic tenderness and induration). In order to avoid bias in his/her assessment, the investigator will not reference the subjects' e-Diary data or CPSSS Section 1.

Each individual component of the CPSSS will be scored on a scale of 0 to 3 (0 = None; 1 = Mild; 2 = Moderate; 3 = Severe). For DYSP, the choice of "Not Applicable" applies to subjects not sexually active for reasons other than endometriosis pain. Responses of "Not Applicable" for the assessment of DYSP will be treated as missing values and will not be included in the summaries/analyses. The total CPSSS has a maximum possible value of 15 (total score range: 0 to 15, lower score indicates less signs and symptoms of endometriosis).

Refer to Section 10.9 for the template.

8.12 Health Economics or Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9 Statistical Methods

9.1 Statistical Hypotheses

The primary objective of the study is to evaluate the efficacy of HMI-115 for 12 weeks compared with placebo in the management of endometriosis-associated pain. This objective will be addressed by comparing the primary efficacy endpoint between each HMI-115 treatment group and placebo. The null hypothesis is that there is no difference in the mean change of DYS at Week 12 between each HMI-115 treatment group and placebo. All statistical tests will be two-sided and a significance level of 0.05 will be used unless otherwise specified. Multiplicity adjustment will not be employed with respect to the multiple dose groups in this proof-of-concept study. A test will be considered significant if the p-value is less than 0.05. Two interim analysis is planned. More details of the interim analysis are presented in Section 9.5.

The objective will also be addressed by obtaining the point and interval estimates of the mean CFB to Week 12 in the DYS NRS for each HMI-115 treatment group and placebo. In addition, hypothesis test for a statistically significant trend (upward slope) across HMI-115 doses will be performed using the 0.05 significance level.

9.2 Sample Size Determination

152 eligible subjects will be randomly assigned to HMI-115 or placebo group and 136 evaluable subjects for an estimated total of 34 evaluable subjects per treatment groupA sample size of 34 evaluable subjects per treatment group is planned. With an assumption that up to 10% of subjects may prematurely discontinue the study without providing data for efficacy evaluations,

enrollment of approximately 38 subjects per treatment group is planned. With 38 subjects per group, there is an 80% power to detect a 1-point difference in the CFB to Week 12 in DYS NRS *within* a treatment group. This is based on the assumption of a standard deviation (SD) of 2.0 and a paired t-test at the 0.05 alpha level. This sample size is also expected to provide adequate precision in the point estimate and 95% confidence interval (CI) of the CFB for each treatment group.

Because this is a proof-of-concept study, the sample size is planned to provide adequate data to evaluate the efficacy and safety of HMI-115 in the dose range studied. It is not based on power calculation to demonstrate statistically significant difference versus placebo. However, in the context of comparing an HMI-115 treatment group versus placebo (ie, between-group comparison), this sample size will provide 80% power to detect a treatment difference of 1.4 point in the CFB in DYS NRS based on the assumption of SD of 2.0 and a 2-sample t-test at 0.05 significance level.

9.3 Populations for Analyses

For purposes of analysis, the following analysis sets will be used:

Table 9-1 Populations for Analyses

Population (Analysis Set)	Description
Enrolled Analysis Set	All subjects who signed the ICF (including screening failures).
Full Analysis Set (FAS)	This analysis set includes all randomized subjects who take at least one dose of IMP. For the FAS, subjects are assigned to a treatment group based on the randomization schedule, regardless of the treatment actually received. FAS will be used for all efficacy analyses.
Per Protocol Analysis Set (PPS)	The PPS comprises a subset of the FAS who do not have protocol deviations that could significantly affect the results for the primary endpoints. Subjects' inclusion/exclusion from the PP population will be determined and documented prior to the database lock and unblinding. PPS will be used for the primary and secondary efficacy endpoints.
Safety Analysis Set	The Safety Analysis Set consists of all subjects who received at least one dose of IMP. Subjects will be analyzed according to the IMP they actually received. Safety Analysis Set will be used for all safety analyses.
PK Analysis Set	The PK analysis set consists of all subjects in the Safety Analysis Set with at least one drug concentration value and have no major protocol deviation that could significantly impact PK assessment.

Immunogenicity analysis set	The immunogenicity analysis set consists of all subjects in the Safety Analysis Set with at least one immunogenicity value.

All protocol deviations will be reviewed and classified regarding how they affect clinical and analysis outcomes during the Blinded Data Review Meetings. Subjects may be excluded from the PPS and PK Analyses Set.

The FAS will be the primary analysis set for all efficacy analyses and the PPS will be used to demonstrate robustness of results for the primary and secondary efficacy endpoints.

9.3.1 Variables for Stratification of Randomization

This study employs a stratified randomization with two stratification factors: 1) region 2) participation in the intensive PK sampling subset (Yes, No). These stratification factors will be taken into account in the statistical analyses.

9.4 Statistical Analyses

A detailed Statistical Analysis Plan (SAP) will be provided in a separate document. The SAP will be finalized prior to database lock. Below is a description of planned statistical analyses. Further details will be presented in the SAP.

9.4.1 General Considerations

All study data will be summarized by treatment group using descriptive statistics. Unless otherwise specified, for continuous data (e.g., age, weight), descriptive statistics will include the number of subjects with data to be summarized (n), mean, SD, median, minimum (min) and maximum (max). All categorical/qualitative data (e.g., gender, race) will be presented using absolute and relative frequency counts and percentages.

All summaries, statistical analyses, and individual subject data listings described below will be completed using Version 9.4 or later of the SAS software (SAS Institute, Inc. Cary, NC).

9.4.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively by treatment group for the FAS and the Safety Analysis Set.

9.4.3 Estimand

The estimand that corresponds to the primary study objective is the treatment effect of HMI-115 in moderate to severe endometriosis-associated pain in the endometriosis population over 12 weeks if all subjects continue using HMI-115 and did not use rescue medication.

The primary estimand is described by the following attributes:

- Treatment conditions: the treatment condition of interest is HMI-115 at 60 mg, 120 mg, and 240 mg injected Q2W for 12 weeks. Placebo treatment is the control group.

- Population: the population includes women with moderate to severe endometriosis-associated pain. As defined in the protocol-specified inclusion/exclusion criteria reflecting the target study patient population for approval.

- Endpoint: the primary efficacy endpoint is CFB in DYS measured by NRS at Week 12.

- Intercurrent event (ICE):

1. Premature withdrawal from study treatment: this ICE will be handled using hypothetical strategy by assuming subjects who have missing data due to early discontinuation behave similarly to other subjects who completed the study in that treatment group.

Missing average DYS score measured by NRS due to early discontinuation will be imputed by reference-based multiple imputation method (jump to reference) under the missing not at random (MNAR) framework as if subjects were completed the study.

2. At least 15% increase in average pill count of rescue analgesic medications compared to Baseline in the EOT menstrual cycle (definition in Section 9.4.4): this ICE will be handled using composite strategy by assuming subjects have no improvement in their pain intensity, and the DYS at EOT menstrual cycle will be set as baseline average value (baseline observation carried forward, BOCF).

- Population-level summary: the mean change in DYS will be summarized for each treatment group with point estimates (least square mean [LSM] with its associated standard error [SE]) and 95% CIs. Estimated treatment difference (compared for each HMI-115 treatment group against the placebo group) along with corresponding 95% CI will be presented using analysis of covariance models (ANCOVA) with treatment, the randomization stratification factor of region as the fixed effects and baseline DYS as covariate.

Subjects who have missing data due to early discontinuation are assumed to behave similarly to other subjects who completed the study. Sensitivity analyses of the same estimand with different assumptions will be employed to check the robustness of the primary analysis. These sensitivity analyses include mixed-effect model repeated measures (MMRM) method, and the Last Observation Carried Forward (LOCF) method will be used. The details of the sensitivity analyses will be included in the statistical analysis plan.

Because the phase 2 study is the first study of HMI-115 in the endometriosis population in a 12-week duration, this estimand will allow HMI-115 to evaluate the efficacy of HMI-115 in the treatment of moderate to severe endometriosis-associated pain relative to placebo. When the results are available, this effect size will be examined for its clinical significance. A definition of responder who reaches clinically meaningful improvement as measured by DYS will then be defined based on a receiver operating curve (ROC) analysis using PGIC as an anchor. In addition to the anchor-based method, the empirical cumulative distribution function (eCDF) method will also be used to determine the clinically meaningful improvement.

9.4.4 Primary Efficacy Endpoints

The primary efficacy endpoint is the mean change of DYS measured by NRS from Baseline to Week 12.

Measurement of Baseline: The baseline measurements will be derived from the last *complete* menstruation cycle during the Screening Period prior to Day 1.It will be designated as the baseline menstrual cycle and is defined as the interval from the first day of the menstruation to the day before the first day of the next menstruation.

Measurement of Week 12: Because the Week 12 (EOT) visit may or may not occur during menstruation, the measurement of Week 12 will be defined by the following 2 approaches, depending on the scenarios. The objective of these approaches is to capture a complete menstrual cycle and designate it as the EOT menstrual cycle.

- If EOT visit occurs during menstruation, the *EOT menstrual cycle* is defined as the interval that begins from the first day after the end of the previous menstruation to the last day of the menstruation during which the EOT visit occurred. It is expected that the end of this menstruation may be days after the EOT visit.

- If EOT visit occurs outside of a menstruation period, the closest menstruation period to the EOT visit will be identified. This menstrual period may be before or after the EOT visit. In either case, the *EOT menstrual cycle* will begin at the end of the menstruation

period *immediately before* the closest menstruation period to the last day of the closest menstruation period.

The mean change will be summarized for each treatment group with point estimate and 95% CI and will be compared for each HMI-115 treatment group to the placebo group using analysis of covariance models (ANCOVA) with treatment, the randomization stratification factor of region as the fixed effects and baseline DYS as covariate. In addition, a mixed-effect model repeated measures (MMRM) method with treatment, the randomization stratification factor of region, and visit as the main effects, and treatment-by-visit interaction will be used as a sensitivity analysis.

The use of rescue medication will be taken into account in the analysis of the primary endpoints. In the ANCOVA analysis, if a subject has at least 15% increase of rescue medication use (in terms of medication counts) compared to baseline in the EOT menstrual cycle, the measurement for Week 12 will be imputed with the baseline NRS measurement (i.e. assuming no improvement from baseline). In the MMRM analysis, if a subject has at least 15% increase of rescue medication use at a particular visit compared to baseline, the measurement at that visit will be imputed with the baseline NRS measurement. Such subjects will also be considered non-responders in the PGIC responder analysis for that visit. The visit window for the MMRM analysis will be defined in the SAP.

In addition to rescue medications, all analgesic medications taken to treat pain other than endometriosis-associated pain will be captured as concomitant medications. The pain intensity NRS measurement for endometriosis-associated pain in the days when these concomitant pain medications are used will be considered unevaluable and will be imputed by the corresponding average baseline measurement (i.e. assuming no improvement from baseline on those days).

To study the dose-response relationship, the CFB to Week 12 will be plotted versus dose. A simple linear regression model will be fitted as a function of dose to characterize the dose-response relationship. In case of lack-of-fit of the simple linear regression model, multivariate or non-linear regression models may be explored.

9.4.5 Secondary Efficacy Endpoints

Efficacy

The analysis methods for the secondary endpoints are summarized in the table below. Details of model specifications and sample SAS codes will be presented in the SAP.

Measurement of Week 24: Because the Week 24 (EOS) visit may or may not occur during menstruation, the measurement of Week 24 will be defined by the following 2 approaches, depending on the scenarios. The objective of these approaches is to capture a complete menstrual cycle and designate it as the *EOS menstrual cycle*.

- If EOS visit occurs during menstruation, the *EOS menstrual cycle* is defined as the interval that begins from the first day of the previous menstruation to the day before the first day of the menstruation during which the EOS visit occurred.

- If EOS visit occurs outside of a menstruation period, the *latest* menstruation period prior to the EOS visit will be identified. The *EOS menstrual cycle* will begin at the end of the menstruation period *immediately before* the latest menstruation period to the end of the latest menstruation period.

Secondary Endpoints	**Analysis Methods**
Change of NMPP measured by NRS from Baseline to Week 12 and 24	ANCOVA and MMRM methods as used for the primary endpoint.
CFB in the monthly mean Endometriosis Daily Impact Pain Scale for DYS, NMPP and DYSP at Week 12 and 24	ANCOVA and MMRM methods as used for the primary endpoint.
Change of DYS measured by NRS from Baseline to Week 24	ANCOVA and MMRM methods as used for the primary endpoint.
Change of DYSP measured NRS from Baseline to Week 12 and 24	ANCOVA and MMRM methods as used for the primary endpoint.
CFB by visit in permitted rescue medication use	The number of medication and the percentage of days that permitted rescue medication is used will be summarized as two separate endpoints. Depending on the frequency of use

Secondary Endpoints	Analysis Methods
	of permitted rescue medications, treatment comparison may be compared using an ANOVA with treatment and region as the main effects. The correlation between the use of rescue medications and the DYS and NMPP NRS will be explored by summary statistics and graphical presentations.
Change in menstrual period heaviness (bleeding) from Baseline by visit	The number and percentage of subjects in each category will be summarized by treatment group for baseline and each visit. Descriptive statistics for the percentage of days subjects had any uterine bleeding will be presented.

9.4.6 Handling of Missing Values

For the analyses using MMRM, missing data will not be imputed. Subjects with missing data will not be excluded from the MMRM analysis. The validity of the missing-at-random (MAR) assumption for the MMRM model will be assessed when interpreting the analysis results. For other analyses, the Last -Observation -Carried -Forward (LOCF) method will be used for post-baseline measurements. For subjects who prematurely discontinue before Week 12, the available observation corresponding to the last post-baseline visit will be carried forward to subsequent visits. Only the available observations in follow-up can be carried forward to Week 24.

9.4.7 Pooling of Investigator Centers

Data from all investigator sites will be pooled for analysis. The analyses will not be performed by center and will not include adjustment for centers.

9.4.8 Safety Analyses

9.4.8.1 IMP Exposure

Duration of exposure to IMP will be summarized descriptively for each treatment group.

9.4.8.2 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment-emergent AEs (TEAE) will be summarized for each treatment group. TEAEs are defined as AEs with a start date on or after the first dose of IMP. Frequencies and percentages of subjects with TEAEs will be calculated for each treatment group as follows:

- Any event
- By system organ class, preferred term and relationship
- By system organ class, preferred term and maximum severity
- Any event and by system organ class and preferred term for events resulting in death
- Any event and by system organ class and preferred term for events resulting in IMP discontinuation
- Any event and by system organ class and preferred term for serious adverse events
- Events of special interest (refer to Section 10.3.1)

A listing by treatment group of TEAEs grouped by body system, and preferred term with subject ID numbers will be generated. Listings of all treatment-emergent SAEs, AEs leading to death, and AEs leading to discontinuation will be generated.

9.4.8.3 Vital signs (BP, pulse, body temperature, and RR)

Vital signs will be summarized descriptively for each treatment group at each visit. The within-group changes from baseline to each visit will be summarized and will be tested with a paired t-test for continuous measurements. The between-group difference will be compared with an ANOVA. Two-sided 95% CI will be constructed for the differences between each of the treatment groups and the placebo group in CFB.

9.4.8.4 Physical examinations

Physical examination findings will be summarized by treatment group and body system. Frequency counts and percentages will be presented.

9.4.8.5 Twelve-lead electrocardiogram (ECG)

ECG parameters, i.e., heart rate (HR), RR, PR, QRS, QTcF, and QTcB will be summarized descriptively for each treatment group at each visit. The within-group changes from baseline to each visit will be summarized and will be compared with a paired t-test for continuous

measurements. The between-group difference will be compared with an ANOVA. Two-sided 95% CI will be constructed for the differences between each of the HMI-115 treatment groups and the placebo group in CFB. The number and percentage of subjects with other clinically significant ECG findings will also be summarized by treatment group at each visit.

9.4.8.6 Clinical laboratory tests

Clinical laboratory test results will be summarized descriptively for each treatment group at each visit. The within-group changes from Baseline to each visit will be summarized and will be compared with a paired t-test for continuous measurements. The between-group difference will be compared with an ANOVA. Two-sided 95% CI will be constructed for the differences between each of the treatment groups and the placebo group in CFB. Shift tables for changes from Baseline according to the normal minimum and maximum will be provided for each laboratory parameter.

9.4.8.7 DXA scan

Bone mineral density data from dual energy X-ray absorptiometry (DXA) scan will be summarized descriptively for each treatment group at each visit. The within-group changes from baseline to each visit will be summarized and will be compared with a paired t-test for continuous measurements. The between-group difference will be compared with an ANOVA. Two-sided 95% CI will be constructed for the differences between each of the HMI-115 treatment groups and the placebo group in CFB.

9.4.8.8 TVU Assessments

TVU data will be summarized descriptively for each treatment group at each visit. Changes from baseline in the number and/or size of ovarian cysts, changes in endometrial thickness will be summarized. Abnormal findings will be listed and discussed.

9.4.8.9 Concomitant Medications

Concomitant medication usage will be summarized by the number and proportion of subjects in each treatment group. The World Health Organization Drug Dictionary (WHO DD) will be used to classify prior and concomitant medications by therapeutic class and generic name based on Anatomical Therapeutic Chemical Classification System (ATC) code level 3. Subjects will only be counted once in each unique ATC Class and generic name if multiple drugs are used by a subject.

9.4.9 Exploratory Analyses

Quality of life:

Quality of Life will be assessed with the HRQoL (Endometriosis Health Profile-5 [EHP-5]). EHP-5 data will be summarized descriptively by treatment group at each visit and will be compared using the MMRM and ANCOVA methods as used in for the primary endpoint.

PGIC:

The number and percentage of subjects in each PGIC response category will be summarized at each visit by treatment group. Statistical comparisons between each HMI-115 treatment group and placebo group in mean scores at each visit will be performed using ANOVA with treatment group as the fixed effect.

The percentage of subjects with response of "Much Improved" or "Very Much Improved" will be summarized at each visit by treatment group, and comparison will be made between each HMI-115 treatment group and placebo group using a chi-square test.

PK analysis:

The following parameters will be calculated for the extensive PK subset and will be reported in the clinical study report together with listing of sparse sampling:

- C_{max}, $C_{through}$, t_{max}, $AUC_{(0\text{-}tau)}$, $t_{1/2}$ following last dose
- AR for both C_{max} and AUC

Phoenix® WinNonlin® Version 8.2 or later will be used to calculate PK parameters using non-compartmental model according to the actual blood collection time.

The descriptive statistics of plasma concentrations will be made based on scheduled sampling time, and individual, average and median concentration-time curves will be separately plotted. PK parameters (extensive PK subset) will be summarized in descriptive statistics (mean, median, SD, minimum and maximum, coefficient of variation [CV%], geometric mean [GM] and geometric coefficient of variation [gCV%]).

A population pharmacokinetic (popPK) model might be developed using all available PK data. The data analysis plan will be described in a separate document from the SAP, and the results will be reported separately from the clinical study report.

PK-PD relationship:

An exploratory analysis of the relationship between HMI-115 plasma concentration/exposure (C_{max}, C_{trough} and/or $AUC_{(0\text{-}tau)}$) and pelvic pain score measured by NRS (cyclic, non-cyclic, and average) as well as the side effects will be performed. Exposure parameters available for each subject from the non-compartmental (NCA) PK analysis or the raw PK data will be compared among the three groups of pelvic pain score and values of side effects. Further details will be provided in the SAP. In addition, the exposure-response relationship between HMI-115 exposure and efficacy and exposure and safety data might be explored by means of population PK-PD analyses. If a population PK-PD analysis is performed, the data analysis plan for the population PK-PD analyses will be described in a separate document from the SAP, and the results will be reported separately from the clinical study report.

Immunogenicity:

- Anti-drug antibody (ADA) and Neutralizing antibody (NABs) will be summarized descriptively for each group at each visit.

9.5 Interim Analyses

In addition to the ongoing safety data monitoring, two unblinded interim analyses of the efficacy data are planned. The first interim analysis will be performed after 60 subjects completed Week 12 visits. The second interim analysis will be performed when 100 subjects completed Week 12 visits. The objective of the interim analyses is to provide preliminary data for the planning of subsequent development activities, and no adjustment of significance level will be employed. The statistical hypotheses tests for the final analysis will be performed at the 0.05 level as described in Section 9.1. These interim analyses will be performed following an interim SAP and will be conducted by an analysis team that is independent from the study team responsible for the study conduct and the final analysis.

9.6 Data Monitoring Committee (DMC)

In order to monitor and protect the safety of study subjects, an independent DMC will be established to review all study data pertaining to subjects' safety on regular basis to adjudicate the overall safety of the subjects in this study. The DMC will convene to provide recommendations on study design and IMP based on review of unblinded safety data. In addition, ad-hoc DMC meetings may be called by the Sponsor at any time for review of newly identified safety concerns. Refer to the DMC Charter for further details.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
    - Applicable ICH Good Clinical Practice (GCP) Guidelines.
    - Applicable regional and local laws and regulations.
    - Regional subject data protection laws and regulations.
    - USA Federal Regulations, as applicable.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The Investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures.
    - Overall conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/IEC, and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the subject or her legally authorized representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative. Subjects who are rescreened are required to sign a new ICF.

The ICF will contain a separate section (or in some cases a separate ICF for optional samples) that addresses the use of remaining mandatory samples for optional exploratory research (if applicable). The Investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research if applicable. Subject who declines to participate will not provide this separate signature.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

10.1.4 Data Protection

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.

The subject must be informed that her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees Structure

The DMC will consist of two unblinded experts in the fields of gynecology and one independent unblind biostatistician. Details refer to DMC charter.

10.1.6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

10.1.7 Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. Monitoring details describing strategies e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies, methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.
- All data generated by the site personnel will be captured electronically at each study site using eCRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.
- If additional corrections are needed, the responsible monitor or data manager will raise a query in the electronic data capture (EDC) application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the eCRF will be frozen.
- The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.

10.1.8 Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

E-Dairy source data will come from electronic device and be interfaced into EDC.

10.1.9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of subject.

The first act of recruitment is the first site open and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further IMP development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.10 Publication Policy

The data and information generated in this study are the exclusive property of the Sponsor and are confidential. Written approval from the Sponsor is required prior to disclosing any information related to this study. Publication of the results will be based on appropriate analyses and review of the completed data. Authorship will be determined based on ICMJE criteria. Publication of any data of this clinical trial without prior Sponsor approval is not permitted.

10.1.11 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor

must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). In the US: Following approval, the protocol amendment(s) will be submitted to the IND under which the study is being conducted.

Administrative changes (not affecting the subject benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

10.1.12 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance cover in accordance with all legal requirements. The civil liability of the Investigator, the persons instructed by him or her and the hospital, practice, or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for subjects participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

10.1.12.1 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare eCRF entries and individual subject's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained.

Checking of the eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures CRO and the Sponsor of the necessary support at all times.

10.2 Appendix 2: Clinical Laboratory Tests

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 10-1. Protocol-Referred Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	• Platelet count • Hemoglobin • WBC Count (absolute) • Erythrocytes • Reticulocytes	• Hematocrit • MCV • MCH	**WBC Differential:** • Neutrophils • Lymphocytes • Eosinophils • Monocytes • Basophils
Coagulation	• PT • Fibrinogen	• INR	• APTT
Clinical Chemistry[#]	• BUN • Creatinine • Glucose, fasting • Sodium • Total protein • Magnesium	• Potassium • Chloride • Calcium • Albumin • GGT • Total bilirubin	• AST (SGOT) • ALT (SGPT) • Alkaline phosphatase
Urinalysis	• Protein • Glucose • Urobilinogen	• Leucocytes • Erythrocytes • Bilirubin	• pH • Ketone • Nitrite • Specific gravity
Sex Hormone	• PRL[*] • DHEAS[*]	• LH[*] • FSH[*]	• Estradiol[*] • Progesterone[*] • Testosterone*
Additional Chemistry [#]	• FT3, FT4, TSH	• CA−125	• GH
Viral serology	• Anti-HAV • HBs Ag • HBc Ab	• Anti-HCV • HCV RNA (for positive or equivocal anti-HCV)	• HIV antigen • Anti-HIV(1+2)
Bone Biomarkers[#] (exploratory)	• CTX	• P1NP	• BSAP
Other tests	• eGFR (using CKD EPI formula) • Pregnancy test (serum pregnancy test at Visit 1 only, urine pregnancy test thereafter)		

Laboratory Assessments	Parameters
	• Urine drug screen: amphetamine, barbiturates, benzodiazepines, tetrahydrocannabinol, cocaine, methadone, methamphetamine, opiates, phencyclidine, and tricyclic antidepressants

ALT = alanine transaminase; anti-HAV = hepatitis A virus antibody; anti-HCV = hepatitis C virus antibody; anti-HIV = human immunodeficiency virus antibodies; APTT = activated partial thromboplastin time; AST = aspartate transaminase; BSAP = bone specific alkaline phosphatase; BUN = blood urea nitrogen; CKD EPI = Chronic Kidney Disease Epidemiology Collaboration CA-125 = cancer antigen-125; COVID-19 = coronavirus disease 2019;CTX = C-terminal telopeptide of type I collagen; FSH = follicle-stimulating hormone; FT3= Free triiodothyronine; FT4= Free thyroxine; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyl transferase; GH=growth hormone; HBsAg = hepatitis B virus surface antigen; HBcAb = Hepatitis B core antibody; DHEAS = Dehydroepiandrosterone-sulfate; INR = international normalized ratio; LH = luteinizing hormone; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; P1NP = procollagen type 1N-terminal propertied; PRL = Prolactin; PT = prothrombin time;SGOT = serum glutamic-oxaloacetic transaminase; SGPT = Serum glutamic pyruvic transaminase; TSH = thyroid stimulating hormone; WBC = white blood cells.
* Sex hormone samples will be collected at the menses cycle days 1 to 5. **Subjects should not take any opioids 2 days prior to blood sampling for PRL**.
# Samples will be collected under morning fasting conditions.

A certified central laboratory will be utilized to process and provide results for all blood tests. Serum pregnancy test will be performed at Visit 1, urine pregnancy test will be performed at Visit 3, 5, 7, 9 and 10 thereafter. Appropriate certifications and laboratory reference ranges will be collected. Instructions regarding the collection, processing and shipping of these samples will be provided by the central laboratory selected for this study. Blood draws should be performed before vital signs, ECG recordings and physical examinations at visits.

The central laboratory results (except PRL, PK and ADA parameters) will be provided by the central laboratory to the study sites where they will be reviewed, signed and dated by the investigator. For any value outside of the reference range, the investigator will indicate on the report if the result is clinically significant (CS) or not clinically significant (NCS).

Investigators must document their review of each laboratory safety report. Laboratory results that could unblind the study will not be reported to study sites or other blinded personnel until the study has been unblinded.

Repeated tests for safety monitoring could be performed locally if needed.

High-dose biotin supplements (e.g., Vitamin B7 or H and coenzyme R and multivitamins) ingestion may interfere with some of the above laboratory tests and should be avoided at least 72 hours prior to blood collections.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study subject, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • In clinical studies, an AE can include an undesirable medical condition occurring at any time, including screening or follow-up periods, even if no study intervention has been administered. • *NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.*

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (e.g., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Adverse Events of Special Interest (AESI)

- Adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and notification by the Investigator to the Sponsor is required.
- AESIs may be modified during a study by protocol amendment, which will enable the Sponsor to collect additional information to better assess any potential and identified risks during the development surveillance.
- The role of the DMC in the handling of these AESIs will also be considered.
- The AESI to be defined in this study includes:
  - Galactorrhea is the spontaneous discharge of milk or a milk-like secretion from the breast in the absence of parturition or beyond six months' post-partum in a non-breastfeeding woman. The secretion may be intermittent or persistent, scant or abundant, free-flowing or expressible, and unilateral or bilateral. An inquiry and breast examination can provide important clinical findings of subjects with galactorrhea.
  - Change in menstrual cycles with oligo- or amenorrhea is defined as no bleeding or spotting in a 56- day interval.
  - Hirsutism is a condition in subjects with excessive growth of dark or coarse hair in a male-like pattern —face, chest, abdomen and back.
  - Acne involves whiteheads, blackheads or pimples that usually appears on the face, forehead, chest, upper back and shoulders.
  - Palpitations are feelings of having a fast-beating, fluttering or pounding heart, or single forceful or skipped beats that not caused by emotional or physical stimulus, exercise, other drugs or food, and cannot be relieved through rest or mental relaxation.
  - Change in mood or behavior includes abnormal thought, speech, and behavior after IMP administration compared with past. Such as mood extremes (depression or mania), new or worsening symptoms of anxiety or depression, and disorganized speech or behavior.

- Infection denotes conditions with immunosuppression. This typically manifests as recurrent, severe, unusual, or opportunistic infections.

- • Constant or severe headache that is distinctly different in quality from usual headaches, and may be worse at night or in the early morning, including newly happened or worsening dull, "pressure-type" headaches, sharp or "stabbing" pain. They can be localized to a specific area or generalized. They can be made worse with coughing, sneezing or straining.
  - Change in vision (and particularly loss of peripheral vision) includes dim, dark, or blurred vision or diminished peripheral vision in one or both eyes or double vision or diminished peripheral vision on one or both sides, etc.

  Theoretically, PRLR blockage will increase PRL and may impact hormone excretion, however PRLR already has been blocked and it is unlikely increased PRL making functional work. Even though risks are more conceptional but need to monitor carefully during study period.

Symptoms of dopamine withdrawal

By blocking PRLR, HMI-115 will increase PRL secretion which may subsequently trigger dopamine release from hypothalamus. Any symptoms of dopamine withdrawal that have been reported after discontinuation of treatment, including apathy, anxiety, depression, fatigue, sweating and pain should be monitored. Theoretically however, PRLR on the dopamine releasing neuron is blocked, it is very unlikely that dopamine releasing will be triggered.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective intervention of a pre-existing condition that did not worsen from Baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive intervention in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- Adverse event questioning will include specific questions regarding symptoms of COVID-19: fever, cough, dry throat, difficulty breathing.
- Confirmed and suspected SARS-CoV-2 infection and COVID-19 will be recorded as AEs.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that is incapacitating with inability to work or do normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study intervention:

Reasonable Possibility:

After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information) to suggest a causal relationship.

No Reasonable Possibility:

After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **insufficient** evidence (information) to suggest a causal relationship.

- For causality assessments, events assessed as having a reasonable possibility of being related to the study intervention will be considered "associated." Events assessed as having no reasonable possibility of being related to study intervention will be considered "not associated." When the event is causality assessment impossible and cannot rule out causality, e.g., insufficient case data, the event will also be considered associated and revised if appropriate when accessible.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • During the course of the study, new or updated information will be recorded in the originally completed eCRF. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information. • Any AEs that are unresolved at last visit in the study are followed up by the Investigator for as long as medically indicated but without further recording in eCRF. For any subject with ongoing AE(s)/SAE(s) at the end of the study, the Sponsor retains the right to request additional information if judged necessary.

10.3.4 Reporting of SAE

SAE Reporting to Sponsor
• The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the SAE paper CRF in order to report the event within 24 hours. Notification by email with scanned copy of the SAE paper CRF or facsimile transmission of the SAE paper CRF to the SAE coordinator is acceptable. • The site will enter the SAE data into the electronic system as soon as it becomes available. • The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the Sponsor (or Sponsor's designated agent) will evaluate the seriousness and the causal relationship of the event to study intervention. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the reference document (Investigator Brochure or Summary of Product Characteristics). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the SAE coordinator by email or fax.

Suspected Unexpected Serious Adverse Reactions (SUSARs)

Any AE that is serious, associated with the use of the IMP, and unexpected (SUSAR) has additional reporting requirements, as described below.

- If the SUSAR is fatal or life-threatening, associated with IMP, and unexpected, regulatory authorities and IECs will be notified within seven calendar days after the Sponsor learns of the event. Then followed by as complete a report as possible within 8 additional calendar days.
- If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with the IMP, and unexpected, regulatory authorities and IECs will be notified within 15 calendar days after the Sponsor learns of the event.

The Sponsor (or Sponsor's designated agent) will notify the Investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of subjects. Follow-up information may be submitted if necessary.

The Sponsor (or Sponsor's designated agent) will also provide annual safety updates to the regulatory authorities and IECs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

The minimum information required for an initial report is:

- Name of person sending the report (e.g., name, address of Investigator);
- Subject identification (screening/randomization number, initials, NOT subject name);
- Protocol number;
- Description of SAE;
- Causality assessment, if possible.

After receipt of the initial report, the Sponsor (or Sponsor's designated agent) will review the information and, if necessary, contact the Investigator, to obtain further information for

assessment of the event. The Sponsor (or Sponsor's designated agent) will be responsible for all information processing and reporting according to local legal requirements. Where necessary, Investigators will inform regulatory authorities in their own countries.

10.4 Appendix 4: Contraceptive Guidance

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal, unless permanently sterile. All subjects in this study are WOCBP and must follow the contraception requirements below. This includes women with tubal infertility from endometriosis.

Exception: Women who have had a documented bilateral salpingectomy or bilateral tubal ligation may participate in the study, but do not have to follow protocol-specified contraception requirements.

Note: Documentation of bilateral salpingectomy can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

Contraception Requirements
A woman is eligible to participate in the study if she meets one of the following criteria:

- Is heterosexually abstinent;

Note: Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.

OR

- Is heterosexually active and agrees to use two forms of the following contraception methods consistently and correctly during the protocol-defined time frame in inclusion and exclusion criteria:
    - Condoms used with spermicide (cream, spray, foam, gel, suppository, or polymer film) or Phexxi
    - Diaphragm used with spermicide (condom may or may not be used) or Phexxi
    - Cervical cap used with spermicide (condom may or may not be used) or Phexxi
    - Vaginal sponge impregnated with spermicide or Phexxi; used with a condom

Note: Hormonal contraception except for sporadic use of emergency contraception is not permitted during the study. Male and female condoms should not be used at the same time.
OR
- Has undergone bilateral tubal sterilization or bilateral salpingectomy;
OR
- Has a vasectomized partner.

Note: Partner must be the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, a two-forms method of contraception must be used.

Subjects should avoid pregnancy from signing the consent until the completion of the study or 3 months after the last dose of IMP, whichever is longer.

Pregnancy Testing: Study subjects should only be included after a negative serum pregnancy test at Visit 1 and a negative urine pregnancy at Visit 3. Urine pregnancy testing to be done at Visit 3, 5, 7, 9 and 10 through home pregnancy test kit. It will be under the supervision of investigators and the results will be recorded in source documents, then collected in EDC.

10.5 Appendix 5: Washout Intervals

Therapy	Minimum Interval for Washout*
Hormonal/Anti-Hormonal Therapy	
Medroxyprogesterone Acetate (Depo-Provera®)	10 months prior to Visit 1
GnRH Agonist – 3 months depot (Lupron®, Zoladex®)	6 months prior to Visit 1
Injectable hormonal contraception with 3-month duration	6 months prior to Visit 1
Injectable hormonal contraception with 2-month duration	4 months prior to Visit 1
Injectable hormonal contraception with 1-month duration	2 months prior to Visit 1
GnRH Agonist (including 1 month depot)	3 months prior to Visit 1
GnRH antagonist	
Selective Progesterone Receptor Modulators (e.g., Ulipristal acetate)	
Nafarelin acetate (Synarel®)	
Danazol (Cyclomen®)	
Aromatase inhibitors	
Menotropins and human chorionic gonadotropin (hCG)	
Oral Contraceptives**	1 months prior to Visit 1
Oral, transdermal or intravaginal Estrogen Preparations	
Oral, intravaginal or transdermal progesterone/progestin Preparations (except Levonorgestrel 1.5 mg)	
Hormonal and Non-Hormonal IUD, sub-dermal progestin implant (e.g., Nexplanon®)	Removal at least 1 month prior to Visit 1
NuvaRing®	
Analgesics	
Non-steroidal anti-inflammatory drugs (NSAIDs) (e.g. aspirin) COX-2 inhibitors Other non-specified analgesics (e.g. acetaminophen or paracetamol)	1 day prior to Visit 2
Opioid analgesics (e.g. tramadol and tapentadol)	5 days prior to Visit 1, no more than 14 days of continuous use within 6 months
Medications that affect PRL level	

Therapy	**Minimum Interval for Washout***
Antipsychotics and antidepressants: Sulpiride, Risperidone, Haloperidol, Clomipramine, Phenothiazines, Nomifensine, etc.	1 months prior to Visit 1
Antiepileptic or anticonvulsant: Diazepam, Phenytoin Sodium, Phenobarbital, etc.	
Injection use of Histamine H1/H2 receptor antagonists: Promethazine, Famotidine, etc.	
Other medications that affect PRL level: Bromocriptine, Cabergoline, Lergotrile, Lisuride, Metergoline, Quinagolide, Terguride, Isoniazide, Domperidone, Metoclopramide, Methyldopa, Reserpine, etc.	
Others	
Herbal remedies containing Hypericum perforatum (e.g. Kava kava and St. John's wort)	At Visit 1
Cannabinoids	1month prior to Visit 1
Growth hormone replacement Anti-tumor necrosis factor (TNF)/anti-nerve growth factor (NGF)	2 months prior to Visit 1

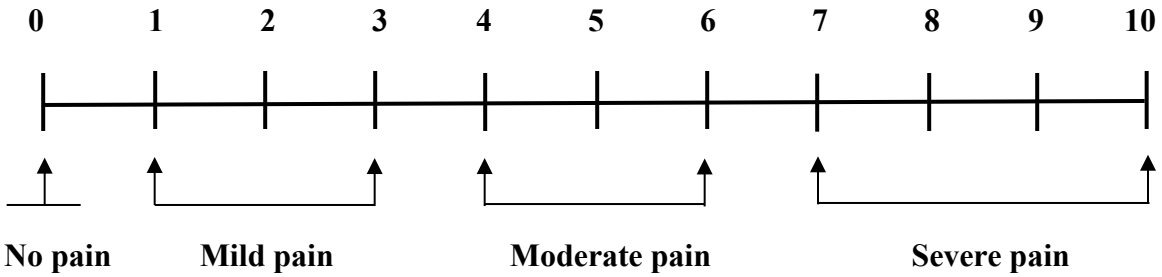
* This is the minimum washout; however, subjects may not enter Screening until return to one normal menstrual cycle.

** Subjects must complete the mandatory month of washout from oral contraceptives and subsequently have a menses/period. Bleeding due to withdrawal of the oral contraceptives cannot be considered the required menses/period.

If the type of medications and the length of Washout are not listed in the table above, consult the Hope Medicine Medical Monitor for a recommendation.

Note: The drugs above should not be withdrawn by the investigator if used for treatment purposes, but rather the washout period may be used if the prescriber recommends discontinuation of any of these drugs.

10.6 Appendix 6: Numeric Pain Rating Scale (NRS)



10.7 Appendix 7: Patient Global Impression of Change (PGIC)

Since I started taking the IMP, my endometriosis related pain has:

☐ Very much improved

☐ Much improved

☐ Minimally improved

☐ Not changed

☐ Minimally worse

☐ Much worse

☐ Very much worse

10.8 Appendix 8: Endometriosis health profile (EHP-5)

PART 1: CORE QUESTIONNAIRE
DURING THE LAST 4 WEEKS, HOW OFTEN, BECAUSE OF YOUR ENDOMETRIOSIS, HAVE YOU...

		Never	Rarely	Sometimes	Often	Always
1.	Found it difficult to walk because of the pain?	☐	☐	☐	☐	☐
2.	Felt as though your symptoms are ruling your life?	☐	☐	☐	☐	☐
3.	Had mood swings?	☐	☐	☐	☐	☐
4.	Felt others do not understand what you are going through?	☐	☐	☐	☐	☐
5.	Felt your appearance has been affected?	☐	☐	☐	☐	☐

Please verify that you have checked one box for each question.

PART 2: MODULAR QUESTIONNAIRE
DURING THE LAST 4 WEEKS, HOW OFTEN, BECAUSE OF YOUR ENDOMETRIOSIS, HAVE YOU...

		Never	Rarely	Sometimes	Often	Always
A.	Been unable to carry out duties at work because of the pain? ***If not relevant, please check here*** ☐	☐	☐	☐	☐	☐
B.	Found it difficult to look after your child/children? ***If not relevant, please check here*** ☐	☐	☐	☐	☐	☐
C.	Felt worried about having intercourse because of the pain? ***If not relevant, please check here*** ☐	☐	☐	☐	☐	☐
D.	Felt the doctor(s) think it is all in your mind? ***If not relevant, please check here*** ☐	☐	☐	☐	☐	☐
E.	Felt frustrated because treatment is not working? ***If not relevant, please check here*** ☐	☐	☐	☐	☐	☐
F.	Felt depressed at the possibility of not having children/more children? ***If not relevant, please check here*** ☐	☐	☐	☐	☐	☐

Please verify that you have checked one box for each question.

10.9 Appendix 9: Composite Pelvic Signs and Symptoms Score (CPSSS)

A. Non-Menstrual Pelvic Pain None 0 Mild 1=Occasional pelvic discomfort Moderate 2=Noticeable discomfort for most of the cycle Severe 3=Requires strong analgesics. Persists during cycle when not menstruating
B. Dysmenorrhea None 0 Mild 1=Some loss in work efficiency Moderate 2=In bed part of the day, occasional loss of work efficiency Severe 3=In bed one or more days, incapacitation
C. Dyspareunia Not Applicable Not sexually active for reasons other than endometriosis pain None 0 Mild 1=Tolerated discomfort Moderate 2=Intercourse painful to the point of causing interdiction Severe 3=Avoids intercourse because of pain
Total Pelvic Pain score (A+B+C) None 0 Mild 1-3 Moderate 4-6 Severe 7-9
D. Pelvic Tenderness None 0 Mild 1=Minimal tenderness on palpation Moderate 2= Extensive tenderness on Palpation Severe 3=Unable to palpate because of tenderness
E. Induration None 0 Mild 1=Uterus freely mobile, induration in the cul-de-sac Moderate 2=Thickened and indurated adnexa and cul-de-sac, restricted uterine mobility Severe 3=Nodular adnexa and cul-de-sac, uterus frequently frozen
Total Physical Sign Score (D+E) None 0 Mild 1-2 Moderate 3-4 Severe 5-6
Total Symptom and Sign Severity Score (A+B+C+ D+E) None 0 Mild 1-2 Moderate 3-5 Severe 6-10 very severe 11-15

10.10 Appendix 10.10 Procedures that allowed to be repeated during screening period

Procedures	Repeat timeframe	Precautions
Blood pressure	Could be repeated once with the timeframe of ⩽7 days	For those who the abnormal results indicate any ongoing or underlying severe disorder that require further intervention, the repeat examinations may not be appropriate to perform
Hematology		
Coagulation		
Clinical Chemistry		
Urinalysis		
eGFR		
ECG		
Urine drug screen	Could be repeated once upon the investigators' discretion	
TVU	Could be repeated once upon the investigators' discretion	
Cervical cytology	Could be repeated once upon the investigators' discretion	In the case of an unsatisfactory sample only
Body weight	Could be repeated once before having DXA scan	It is for the requirement of DXA equipment

Reasons for the repeat should be documented in detail and the investigator should make the final decision for the eligibility of the subjects based on the repeat outcome.

Note: Repeat procedures is not rescreening. Repeat procedures include but not limited to the upper items as per the investigator's discretion.

10.11 Appendix 11: Abbreviations and Trademarks

ADA	Anti-Drug Antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
APTT	Activated partial thromboplastin time
AR	Accumulation ratio
AST	Aspartate transaminase
ATC	Anatomical therapeutic chemical classification system
$AUC_{(0\text{-}tau)}$	Area under the curve of plasma concentrations vs time for the dosing interval
BMI	Body mass index
BMD	Bone mineral density
BP	Blood pressure
BUN	Blood urea nitrogen
BSAP	Bone specific alkaline phosphatase
CI	Confidence interval
CFB	Change from baseline
COVID-19	Coronavirus disease 2019
CRF	Case report form(s) (paper or electronic as appropriate for this study)
CKD EPI	Chronic kidney disease epidemiology
C_{max}	Maximum concentration
CPSSS	Composite pelvic signs and symptoms score
CRO	Contract research organization
C_{trough}	Concentration before dosing during multiple dose administration
CTX	C-terminal telopeptide of type 1 collagen
CV	Coefficient of variation
DBP	Diastolic blood pressure
DXA	Dual energy X-ray absorptiometry
DHEAS	Dehydroepiandrosterone-sulfate
DMC	Data monitoring committee
DYS	Dysmenorrhea
DYSP	Dyspareunia
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form

eDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EHP-5	Endometriosis health profile-5
ELISA	Enzyme-linked immunosorbent assay
EOT	End of treatment
FAS	Full analysis set
FDA	Food and Drug Administration
FiH	First-in-Human
FT3	Free triiodothyronine
FT4	Free thyroxine
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	Gonadotropin-releasing hormone
HAV-IgM	Hepatitis A Virus Immunoglobulin M
HBsAg	Hepatitis B surface antigen
HBcAb	Hepatitis B core antibody
HCV RNA	hepatitis C virus RNA
ICE	Intercurrent event
ICF	informed consent form
IUD	Intra-uterine device
HIV	Human Immunodeficiency Virus
HIV Ab	HIV Antibody
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
LSM	least square mean
MMRM	Mixed-effect model repeated measures
MRI	Magnetic Resonance Imaging
NAB	Neutralizing antibody
NOAEL	No Observed Adverse Effect Level
NMPP	Non-Menstrual Pelvic Pain
NRS	Numeric Rating Scales
NSAIDs	Non-steroidal anti-inflammatory drugs

P1NP	Procollagen type 1N-terminal propertied
PD	Pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic(s)
POPPK	Population pharmacokinetics
PPS	Per protocol analysis set
PRL	Prolactin
PRLR	Prolactin receptor
PVC	Premature ventricular contraction
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's correction formula
QTcF	QT interval corrected for heart rate using Fridericia's correction formula
Q2W	Once every two weeks
Q4W	Once every 4 weeks
RT-PCR	Real-time reverse transcriptase polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SoA	Schedule of activities
RNA	Ribonucleic acid
SBP	Systolic blood pressure
s.c.	Subcutaneous
SAE	Serious adverse event
SAP	Statistical analysis plan
SERM	Selective estrogen receptor modulators
SoA	Schedule of activities
SS	Steady state
SUSAR	Suspected unexpected serious adverse reaction
TOC	Table of contents
$T_{1/2}$	Elimination half-life
T_{max}	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration
TVU	Transvaginal ultrasound
USA	United States of America
V	Visit
WHO	World Health Organization
WOCBP	Woman of childbearing potential

Declaration of the Investigator

Title: A Randomized, Multicenter, Double-Blind, Placebo-Controlled Phase 2 Study to Evaluate the Safety and Efficacy of HMI-115 in Women with Moderate to severe Endometriosis-Associated Pain Over a 12-Week Treatment Period.

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, CRFs/ electronic CRF (eCRF), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethic Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the subjects.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the Local Study Center

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

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12 Revision History

Sections	Change	Rationale
Version 5.0 to Version 6.0		
1.1 Synopsis **3.Objectives and Endpoints**	Safety and tolerability endpoints 7 from "CFB in Bone mineral density by Dual energy X-ray absorptiometry (DXA) scan at week 12" to "CFB in Bone mineral density by Dual energy X-ray absorptiometry (DXA) scan after 12 weeks' treatment (at EOT visit)" Safety and tolerability endpoints 8 from "CFB in transvaginal ultrasound (TVU) index (including number and size of ovarian cyst, thickness of endometrium) at week 12" to "CFB in transvaginal ultrasound (TVU) index (including number and size of ovarian cyst, thickness of endometrium) after 12 weeks' reatment (at EOT visit)"	Keep consistence with the Schedule of Activities (SoA) and avoid ambiguity
1.3 Schedule of Activities (SoA)	Note 8 added excptions "Urine drug screen includes amphetamine, barbiturates *(except for sites in China),* benzodiazepines, tetrahydrocannabinol, cocaine, methadone, methamphetamine, opiates, phencyclidine, and tricyclic antidepressants *(except for sites in China)*.	According to the condition in different countries.

	Added "(Virgins may be exempted per the investigator's discretion)" to note 11. Added "In some circumstances, transrectal or transabdominal ultrasound is allowed per the investigator's discretion." to note 14. Added "(can be adjusted according to the condition of the site)." To note "Blood draws should be performed before vital signs, ECG recordings and physical examinations at visits."	For ethnical reasons and regular clinical operations in different countires. According to the clinical practice of different sites.
9.5 Interim Analyses	A second interim analysis added. "*The second interim analysis will be performed when 100 subjects completed Week 12 visits.* The objective of the interim analyses is to provide preliminary data *for the planning of subsequent development activities,* and no adjustment of significance level will be employed." "~~This interim analysis~~ These interim analyses will be performed *following an interim SAP and* will be conducted by an analysis team that is independent from the study team responsible for the study conduct and the final analysis."	According to the sponsor's dicision
Version 4.0 to Version 5.0		
Sponsor Signatory	Changed the names of signatory	NA

1.1 Synopsis 2.1 Study Rationale 3 Objectives and Endpoints	Removed the part of part 2 in the whole protocol. The study will ~~have two parts: Part 1 and Part 2. Part 1~~ will determine the safety and efficacy of HMI 115 at 60 mg Q2W, 120 mg Q2W, and 240 mg Q2W. ~~Only when the safety and efficacy have been evaluated by the Sponsor in Part 1 of the study will eligible subjects (new subjects) be admitted to Part 2 of the study. Part 2 of the study will determine the safety and efficacy of HMI 115 at 480 mg every 4 weeks (Q4W) and Q2W.~~	According to the sponsor's decision.
	Deleted "F~~or Part 1 and Part 2 of the Study~~"in the "Objectives and Endpoints" form.	Keep consistency with the removal of Part 2 study.
	Changed the description of the secondary endpoints "Safety and tolerability"to 2. *CFB by visit in* v~~V~~ital signs (blood pressure [BP], pulse, body temperature, and respiratory rate [RR]) 3.CFB by visit in p~~P~~hysical examinations 4.*Number and ratio of participants used* c~~C~~oncomitant medication 5.*CFB by visit in* t~~T~~welve-lead electrocardiogram (ECG) 6.*CFB by visit in* c~~C~~linical laboratory tests (hematology, coagulation, clinical chemistry, urinalysis, hormones and CA-125) 7.*CFB in Bone mineral density by* Dual energy X-ray absorptiometry (DXA) scan at week 12	Keep consistency with the statements of primary endpoints

	8.*CFB in* t~~T~~ransvaginal ultrasound (TVU) index *(including n~~N~~umber and size of o~~O~~varian cyst, thickness of endometrium)* at week 12	
1.1 Synopsis 4.1 Study design	Deleted statements of part 1 and part 2 in the "Overall Design" section	Keep consistency with the removal of Part 2 study.
	Deleted statements of part 1 and part 2 in the "Number of Subjects" section	Keep consistency with the removal of Part 2 study.
	Deleted statements of part 1 and part 2 in the "Intervention Groups and Duration" section	Keep consistency with the removal of Part 2 study.
1.2 Schema	Deleted Figure 1-2 Deleted "Part 1" from titile of Figure 1-1	Keep consistency with the removal of Part 2 study.
1.3 Schedule of Activities (SoA) 8.6 Pharmacokinetics	Deleted Part 1 in "SoA for ~~Part 1 of~~ the study"	Keep consistency with the removal of Part 2 study.
	Deleted "Rescue Medication Return for count"	For the clinical practice
	Deleted note 4 and changed the numbers of the notes accordingly	Keep consitency with the deletion of Part 2 study
	Deleted Table 1-2, Table 1-5, Table1-6 and changed the number of the other tables accordingly, including in note 28 (originally 29) and section 8.6.	Keep consitency with the deletion of Part 2 study
1.3 Schedule of Activities (SOA) 7.2 Subject Withdrawal from the Study	Revised the note for PK and ADA sampling: "Note: For subjects discontinued from IMP or withdrawn from study, no additional PK and ADA sampling ~~other than~~ except ~~regular~~EOT and EOS visits (if possible) are~~is~~ required after IMP discontinuation."	For the clinical practice and the meaning of PK and ADA samples for subjects discontinued from IMP or withdrawn from study.
2.3.1 Risk Assessment	HMI-115 will be administered by injection through s.c. route~~ in Part 1 and Part 2 of~~ the study. In ~~Part 1 of~~	Keep consistency with the removal of Part 2 study.

	the study, the subjects will receive injections of HMI-115 (60 mg to 240 mg) or placebo. ~~and in Part 2 subject will receive injections of HMI-115 480 mg or placebo.~~	
2.3.2 Benefit Assessment	Deleted the descriptions for part 1 and part 2 "~~Part 2 of the study will be carried out only if limited effect is observed at the dose of 240 mg Q2W~~ "	Keep consistency with the removal of Part 2 study.
4.2 Scientific Rationale for Study Design	Deleted "~~In addition, data of Part 1 of the study will allow for choosing appropriate doses for Part 2 of the study.~~"	Keep consistency with the removal of Part 2 study.
6.1 Study Intervention(s) Administered	Deleted the projected dose of part 2 in Table 6-1 and deleted the notes for part 1 and part 2 in Table 6-1 and Table 6-2	Keep consistency with the removal of Part 2 study.
6.2 Preparation, Handling, Storage, and Accountability	Added "Requirements for aseptic operation should be followed during IMP preparation." "the reconstituted solution should be stored between 2°C and 8°C…" is revised to "the reconstituted solution should be stored at 2- 8°C or room temperature…". Deleted "If the solution has been stored above 25°C, it must no longer be used for application and should therefore be discarded.	According to updated <Investigational Products Preparation and Administration Instruction for Clinical Trial HMI-115EM201>, Revision 01
8 Study Assessments and Procedures	Deleted Table 2 in " Study procedures and their timing are summarized in the SoA (Table 1-1 ~~and Table 1-2~~)."	Keep consistency with the removal of Part 2 study.
8.1 Efficacy Assessments (for Part 1 and Part 2)	Deleted "~~(for Part 1 and Part 2)~~" in the subtitle of this part	Keep consistency with the removal of Part 2 study.
8.2.7 Dual Energy X-ray	b) If the subject does not meet the criteria for adequate recovery on her	Post treatment DXA may not reflect the effect of HMI-115 on

Absorptiometry （DXA）	DXA scan at post-treatment month 6, refer to a bone specialist ~~perform another DXA scan at post-treatment month 12~~ (Define adequate recovery as change from pre-treatment baseline of > -1.5% at the lumbar spine and > -2.0% at the total hip). c) Refer to a bone specialist those subjects with ~~change from pre-treatment baseline in BMD of ≤ -3.0% at the lumbar spine and/or total hip, and/or~~ Z-score ≤ -2.0 at any anatomic site at post-treatment month ~~12~~ 6 (or on their final DXA scan if they do not follow-up as instructed). The window period for EOT visit and~~,~~ post-treatment month 6 ~~and month 12~~ DXA scan is ±14 days.	BMD, especially after 12 months, because after a subject leaves the study, she will not be prohibited from medications that influence her BMD.
8.3.1 Patient Global Impression of Change (PGIC) Score	Subjects will score the PGIC as shown in the SoA (refer to Table 1-1~~, and Table 1-2~~).	Keep consistency with the removal of Part 2 study.
9.1 Statistical Hypotheses	Added “One interim analysis is planned. More details of the interim analysis are presented in Section 9.5.”	Introduce the interim analysis.
9.2 Sample Size Determination	Deleted the paragraph of sample size for part 2 and revised “152 eligible subjects will be randomly assigned to HMI-115 or placebo group and 136 evaluable subjects for an estimated total of 34 evaluable subjects per treatment group ~~in Part 1. Sample sizes for Part 1 and Part 2 are planned separately~~.”	Keep consistency with the removal of Part 2 study.
9.4 Statistical Analyses	The SAP will be finalized prior to database lock ~~and unblinding of Part 1~~.	Clarify the time for SAP finalization.
9.4.1 General Considerations	All study data will be summarized by treatment group using descriptive	Keep consistency with the removal of Part 2 study.

	statistics ~~for Part 1 and Part 2 of the study.~~	
9.4.3 Estimand	Deleted "~~The intercurrent events considered include 1) use of rescue medication, and 2) missing values during the study, and 3) missing values due to early discontinuation of HMI-115 .~~"	Described with more details in the following paragraphs.
9.5 Interim Analysis	Deleted the original statements and added the interim analysis. "In addition to the ongoing safety data monitoring, one unblinded interim analysis of the efficacy data is planned after 60 subjects completed Week 12 visits. The objective of the interim analysis is to provide preliminary data, and no adjustment of significance level will be employed. The statistical hypotheses tests for the final analysis will be performed at the 0.05 level as described in Section 9.1. This interim analysis will be performed by an analysis team that is independent from the study team responsible for the study conduct and the final analysis."	According to the sponsor's decision
Others	Corrected typographical errors and other minor edits for consistency	NA
Version 3.2 to Version 4.0		
1.3 Schedule of Activities (SoA)	Deleted the test for Covid-19 infection delete footnote 17 and accordingly revised other order numbers	According to the global COVID-19 situation and change in exclusion criteria
	Added "for count" after "Rescue medication return"	Clarify the reason for the rescue medication return

2.3.1 Table 2 1. Risk Assessment	Revised "In the 26-week toxicity study in male and female cynomolgus monkeys treated with 24 and 100 mg/kg of HMI-115 weekly, no HMI-115 related changes were noted in hormone detection (testosterone, estradiol and progesterone) throughout the study." from mitigation strategy to Summary of Data/Rationale for Risk.	Adjust the content to a more proper place
	Clarify the source of "minimal reversible atrophy of the mammary gland".	Clarify the source of this risk
2.3.1.1 Risk Assessment for COVID-19 Pandemic	Modified "Appropriate measures have been implemented into this protocol to ~~detect COVID-19 disease to confirm eligibility of subjects and to~~ safely conduct the study."	According to the change of the exclusion criteria
	Deleted "~~In addition, subjects will be asked if they have been exposure to a person who has tested positive for SARS-CoV-2.~~"	According to the change of the exclusion criteria
5.1 Inclusion Criteria	Added "11. Subject who is willing to limit alcohol consumption during the study to no more than approximately one alcoholic drink or equivalent [beer (354 mL/12 ounces), wine (118 mL/4 ounces), or distilled spirits (29.5 mL/1 ounce)] per day."	According to FDA reviewer's comments
5.2 Exclusion Criteria	Deleted "1. Subject has a positive RT-PCR test for SARS-CoV-2 at the Screening Visit or prior to randomization"	According to the global COVID-19 situation
	Modified the criterion 2 from "Subject has clinical signs and symptoms consistent with SARS-CoV-2 infection, e.g., fever, dry cough, dyspnea, sore throat, fatigue, loss of smell or taste, confirmed with positive SARS-CoV-2 test result within 4 weeks prior to Screening or randomization." to "Subject with confirmed SARS-CoV-2 infection	According to the global COVID-19 situation

	within 2 weeks prior to Screening or randomization.”	
	Deleted “4. Recent (within 14 days prior to screening or randomization) exposure to someone who has COVID-19 symptoms or positive test result”	According to the global COVID-19 situation
	30. Added “has a history of *suicide attempts o*r…”	According to FDA reviewer’s comments and recommendations
5.3.1Prolactin Sampling	Modified this section to “Prior to PRL sampling, the subject must be examined and instructed to avoid PRL influencing factors such as emotional/physical stress, high-protein meals, all forms of chest and breast stimulation, including sexual activity and impact exercises such as running/jogging (these factors should be avoided on the morning prior to blood sampling), or any medication influencing PRL levels (refer to Section 6.5.2).”	Clarify the activities which should be avoided before prolactin sampling and the subject should be instructed to avoid these activities.
5.3.3 Alcohol Restrictions	Deleted this section	Added this criterion to inclusion criteria 11.

6.5.2 Prohibited Medications 10.5 Appendix 5	Added "Cannabinoids" to the list of prohibited medications and added washout period in Appendix 5	According to FDA reviewer's comments
8.2.1 Physical Examinations	Added "(including extra-ocular movements)" in the brief physical examination of HEENT	According to FDA reviewer's comments
8.6 Pharmacokinetics	Added "Plasma samples collected for pharmacokinetics analysis will be retained for up to 5 years following study finalization for possible further characterization of pharmacokinetic profile of HMI-115 at a specialized laboratory."	Clarified the maximum storage time of PK samples.
9.1Statistical Hypotheses	Changed "The null hypothesis is that there is no difference between each HMI-115 treatment group and placebo" to "The null hypothesis is that there is no difference *in the mean change of DYS at Week 12* between each HMI-115 treatment group and placebo."	Make the null hypothesis more clear
9.2 Sample Size Determination	Added "(ie, between-group comparison)," in "However, in the context of comparing an HMI-115 treatment group versus placebo *(ie, between-group comparison),* this sample size will provide 80% power to detect a treatment difference of 1.4 point in the CFB in DYS NRS based on the assumption of SD of 2.0 and a 2-sample t-test at 0.05 significance level."	Clarify or expalain to make it more clear
9.3 Table 9-1 Population for Analyses	The PK analysis set consists of all subjects in the Safety Analysis Set with at least one drug concentration value and ~~adequate data to derive the PK parameters.~~ *have no major protocol deviation that could significantly impact PK assessment*.	Clarify the definition of PK analysis set

9.4.2 Demographics and Baseline Characteristics	Deleted "~~Hypotheses testing may be performed to assess the comparability of demographics and baseline characteristics among the treatment groups.~~"	Will not do this test
9.4.3 Estimand	Added the primary estimand and Intercurrent event(ICE)	Provide more details of Estimand and Intercurrent event
9.4.4 Primary Efficacy Endpoints	**Measurement of** Baseline**:** changed from "The baseline measurement is defined as the average of the last 5 weeks (35 calendar days) during the Screening Period prior to Day 1." to "The baseline measurements will be derived from the *last complete menstruation cycle* during the Screening Period prior to Day 1.It will be designated as the baseline menstrual cycle and is defined as the interval from the first day of the menstruation to the day before the first day of the next menstruation" and provided the two senarios. **Measurement of Week 12:** changed from"The Week 12 measurement will be the average of the last 5 weeks prior to the EOT Visit ." to " Because the Week 12 (EOT) visit may or may not occur during menstruation, the measurement of Week 12 will be defined by the following 2 approaches, depending on the scenarios. The objective of these approaches is to capture a complete menstrual cycle and designate it as the EOT menstrual cycle" and accordingly revised related contents	Make the baseline and primary end point time period more reasonable as fixed duration of 35days may include 1 and a half or two halves of menstrual bleeding periods to evaluate DYS which is the primary endpoint and may not reflect of the real pain of the subjects

9.4.4 Primary Efficacy Endpoints	Deleted ~~"The time frame for a visit for which the rescue medication use will be attributed to is defined as the 5 weeks (35calendar days) preceding the EOT visit for the ANCOVA analysis."~~	According to the change of time frame for EOT menstrual cycle
9.4.5 Secondary Efficacy Endpoints	Added the Measurement of Week 24	Keep consistency with primary endpoints
9.4.6 Handling of Missing Values	For other analyses, the Last Observation Carried Forward (LOCF) method will be used *for post-baseline measurements.* Added "for post-baseline measurements." **Added "**Only the available observations in follow-up can be carried forward to Week 24.**"**	Clarify the method of handling missing values
10.2 Appendix 2: Clinical Laboratory Tests	Modified "Protocol-Required Safety Laboratory Assessments" to "Protocol-Referred Safety Laboratory Assessments"	For the convenience of implementation in different countries
10.3.1 Definition of AE	Modified from "Change in vision (and particularly loss of peripheral vision) includes dim, dark, or blurred vision in one or both eyes or double vision or diminished peripheral vision to both sides, etc." to "Change in vision (and particularly loss of peripheral vision) includes dim, dark, or blurred vision or *diminished peripheral vision* in one or both eyes or double vision or diminished peripheral vision *on one* or both sides, etc.*"*	According to FDA reviewer's comments

10.3.3 Recording and Follow up of AE and SAE	Deleted "potential exposure" in "Adverse event questioning will include specific questions regarding symptoms of COVID 19: fever, cough, dry throat, *and* difficulty breathing~~, and potential exposure in the past 2 weeks~~."	Keep consistency with the exclusion criteria.
	Revised Assessment of Intensity from "Severe: An event that prevents normal everyday activities." to "Severe: An event that is *incapacitating with inability to work* or *do* ~~prevents~~ normal everyday activities."	Wording change to clarify the word prevents and definition of severe AE.
10.10 Appendix 10	Added "Repeat procedures include but not limited to the upper items as per the investigator's discretion." to the note.	To make it more flexible
others	Corrected typographical errors and other minor edits for consistency	NA
Version 3.1 to Version 3.2		
Page 3 sponsor signature	Modified the name of CMO	Corrected the name of CMO
Version 3.0 to Version 3.1		
1.1 Number of Subjects and 9.2 Sample Size Determination	Change from "~~Approximately 190 subjects will be screened to achieve 152 subjects randomly assigned~~" to "152 eligible subjects will be randomly assigned"	The number of screened subjects will depend on the actual situation
1.3 Schedule of Activities (SoA)	Deleted "Medical history, current medical conditions" from Visit 2	Medical conditions after Visit 1 will be collected as AEs

1.3 Schedule of Activities (SoA) and 8.2.1 Physical Examinations	Replaced "complete physical examination" in Visit 3 and Visit 6 with "brief physical examination"	Brief physical examination can meet the requirement for body check during treatment period. This is to simplify the procedure.
1.3 Schedule of Activities (SoA) and 8.2.7 DXA	Changed 1.3 annotation 14 to "Subjects who discontinue from IMP prior to week 11or *become pregnant during the study* does not require a DXA scan" and changed the last paragraph in 8.2.7 to "Subjects who prematurely discontinue IMP treatment prior to week 11 will not have a DXA at the EOT visit *or in the Post-treatment Follow-up Period. Subjects who become pregnant during the study will not have protocol required DXA scans."*	Added clarification that pregnant subjects will not have DXA.
1.3 Schedule of Activities (SoA) and 10.2 Appendix 2: Clinical Laboratory Tests	Deleted "~~Samples of coagulation test should avoid menstrual period.~~" from SOA annotation 18 and table 10-1.	No significant difference in coagulation results between different periods of menstrual cycle have been identified by studies.
2.3.1.1 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Changed "United States Food and Drug Administration (USFDA) has issued new guidelines" to "Both European Medicines Agency (EMA) and United States Food and Drug Administration (USFDA) have issued new guidelines"	Added European countries as new study regions, then added the guideline accordingly.
4.1 Overall Design	Changed from "~~The planned study locations include China and United States of America (USA)~~." to "The planned study *regions* include China, the United States of America (USA) *and European countries*."	Updated to reflect the current study regions and to address the U.S. FDA's comments about specifying the regions by which your randomization will be stratified.
5.1 Inclusion Criteria	Deleted ~~11. Subject who is willing to limit alcohol consumption during the study to no more than approximately one alcoholic drink or equivalent (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day.~~	Moved it to 5.3.3 lifestyle consideration, alcohol restrictions. It is more appropriate to considerate this requirement as subject's education.

5.2 Exclusion Criteria	2. Changed to "Subject has clinical signs and symptoms consistent with SARS-CoV-2 infection; e.g., fever, dry cough, dyspnea, sore throat, fatigue, loss of smell or taste, confirmed with positive SARS-CoV-2 test result within 4 weeks prior to Screening or ~~any time prior to~~ randomization."	To make it clear that the restriction is for 4 weeks prior to screening or 4 weeks prior to randomization to avoid misunderstanding.
	5. Changed from "Subject is …or is less than 6 months post-partum or post-abortion …" to "Subject is … or is less than 6 months post-partum or *3 months* post-abortion …".	For most post-abortion cases, 3 months would be enough to cover the recovery of patient's body condition. And this is the bottom line, the investigators could make decision based on the actual situation.
	14. Change from "Subject has a current history of ~~thyroid dysfunction (hyper , or hypothyroidism)~~" to "Subject has a current history of *hyperthyroidism or uncontrolled hypothyroidism"*.	Hypothyroidism can be controlled by medication and the patients' thyroid function can remain stable for years. Subjects with controlled hypothyroidism can still have reliable study results.
	16. Added " (e.g, congenital immune deficiency syndrome, or currently under immunosuppressive therapy, etc.)" behind "Subjects with immunocompromised status"	To give some examples to help the investigators to understand the requirement better.
	32. Changed to "Subject has a medical history of confirmed psychiatric disorder (e.g., major depression, post-traumatic stress disorder, schizophrenia, bipolar disorder) , or has a history of epilepsy ~~or has suicidal attempt~~, for whom it would not be recommended to stop concurrent medication therapy or may require medication that prohibited during study participation (refer to Section 6.5.2 and 10.5 for prohibited medication and washout period)"	It is not precise to detect suicidal attempt without a specific instrument. It will be based on the investigators' judgment if the subject's mental status is proper for the study. And during the study, the subject's mental status will be strictly monitored.
	34. Changed Z-score from ⩽-2.0 to ⩽ -1.5	To address the U.S. FDA's comments

6.5.1 Rescue Medications Table 6-3	Added “tramadol+ acetaminophen”	To give investigators and subjects more choices and improve the subject’s compliance.
6.5.2 Prohibited Medications and 10.5 Appendix 5: Washout Intervals	Deleted “Thyroxine or Levothyroxine” and “Cannabinoids” from table 6-4 and Appendix 5	To keep consistent with revised exclusion criterion 14 and “Cannabinoids” can be covered by urine drug screen
9.3 Populations for Analyses Table 9-1	Added “Immunogenicity analysis set/ The immunogenicity analysis set consists of all subjects in the Safety Analysis Set with at least one immunogenicity value.” in the table	To add an analysis set
9.4.3Estimand	Added a paragraph to describe the estimand analysis	To address the U.S. FDA’s comments
9.4.4 Primary Efficacy Endpoints	Added the penultimate paragraph to describe how to handle all analgesic medications taken to treat pain other than endometriosis-associated pain in efficacy analysis.	To address the U.S. FDA’s comment about “Capture use of all analgesic medications taken to treat pain other than endometriosis-associated pain (EAP) (e.g. migraine). Describe how you will handle these protocol deviations in your efficacy analysis.”
9.4.5 Secondary Efficacy Endpoints	Added “as two separate endpoints.” To the end of “The number of medication and the percentage of days that permitted rescue medication is used will be summarized”	To address the U.S. FDA’s comment about how to determine the overall use of rescue medication incorporating both components
9.4.8.8 TVU	Changed the content to “TVU data will be summarized descriptively for each treatment group at each visit. *Changes from baseline in the number and/or size of ovarian cysts, changes in endometrial thickness will be summarized. Abnormal findings will be listed and discussed.*”	To address the U.S. FDA’s comment about “In your final clinical study report (CSR), include a summary of findings on transvaginal ultrasound reporting changes from baseline to end of study (e.g., change in the number and/or size of ovarian cysts, changes in endometrial thickness, and other abnormal findings).”
10.3.1 Definition of AE	Changed the definition of “Hirsutism” to “Hirsutism is a condition in subjects with excessive growth of dark or	To address the U.S. FDA’s comments

Adverse Events of Special Interest (AESI)	coarse hair in a male-like pattern — face, chest, *abdomen* and back"	
	Changed the definition of "Palpitations" to "Palpitations are feelings of having a fast-beating, fluttering or pounding heart, or *single forceful or skipped beats* that not caused by emotional or physical stimulus, exercise, other drugs or food, and cannot be relieved through rest or mental relaxation."	
	Changed the definition of "Change in mood or behavior" to "Change in mood or behavior includes abnormal thought, speech, and behavior after IMP administration compared with past. Such as mood extremes (depression or mania), *new or worsening symptoms of anxiety or depression*, and disorganized speech or behavior."	
	Changed the definition of "headache" to "Constant *or severe* headache *that is distinctly different in quality from usual headaches* and may be worse at night or in the early morning, including newly happened or worsening dull, "pressure-type" headaches, sharp or "stabbing" pain. They can be localized to a specific area or generalized. They can be made worse with coughing, sneezing or straining."	
	Changed the definition of "Change in vision" to "Change in vision (and particularly loss of peripheral vision) includes dim, dark, or blurred vision in one or both eyes or *double vision* or reduced *diminished peripheral vision* to both sides, etc."	
Version 2.0 to Version 3.0		

1.1, and 3.0 Objectives and Endpoints/Study Design	Change from "~~Quality of life~~" to "Other patient-reported outcomes"	Made the title more appropriate
1.3 Schedule of Activities (SoA) Table 1-1	Annotation 5, deleted "~~If subjects are discontinued from IMP, all visits and procedures as outlined in the SoA till EOT Visit should be completed. If subjects withdraw from the study during the treatment period, the EOT Visit should be performed as soon as possible and sex hormones collection is not required for subjects not in menses cycle days 1 to 5~~"	For subject who early discontinued from study without withdrawal consent, efforts will be made to retain the subject in the study until follow-up visit.
	Annotation 6, changed from "~~If the subjects withdraw from the study during the follow-up period, the follow-up visit should be performed as soon as possible (sex hormones collection is not required for subjects not in menses cycle days 1 to 5)~~." to "Refer to Section 7.1 and 7.2 for the follow-up requirement for subjects who discontinue from IMP or withdraw from the study."	The detail follow-up visit arrangement has been updated in "Section 7.1 and 7.2"
	Annotation 8, added "after collecting all testing/examination data at each visit (except for Visit3, refer to #22)" just after *IMP will be administered Q2W*	To clarify that IMP administration should be the performed after all scheduled testing/examination completion at each onsite visit
	Annotation 14, Change from "~~IMP discontinuation prior to week 11 does not require a DXA scan.~~" to "Subjects who discontinue IMP prior to week 11 during the study does not require a DXA scan. For more details, including subjects who needs further DXA scan after EOT visit, refer to Section 8.2.7."	Added more clarification for DXA scan.
	Annotation 16, change from "~~(for positive anti-HCV only), and anti-HIV (1+2).~~" to "(for positive or equivocal	Revised to reflect central lab classification for viral serology test

	anti-HCV), and HIV antigen/anti-HIV (1+2)."	
	Annotation 26,added "and additional training will be provided to subjects who have missed data entry." to *e-Diary entries compliance will be assessed*	Update to ensure investigators will take efforts to maintain patient's compliance for e-Diary data entry.
	Annotation 29, added "(not required for those who discontinued from IMP or withdraw from study)."	To specify no additional sampling other than regular visits are required for those who discontinued from IMP
1.3 Schedule of Activities (SoA) Table 1-2	Updated in accordance with Table 1-1	To keep consist with the previous part
2.2 Background	Change from "the IB ~~(Version 1.0, 21 April 2021)"~~ to "the most updated version of IB"	IB have been updated
2.3.1 Risk Assessment Table 2-1	Added 26-week toxicity study result to non-clinical risk part	Added new pre-clinical safety data
4.1 Overall Design	Changed from "~~The planned study locations include China and United States of America (USA)~~." to "The planned study locations include China, the United States of America (USA) and European countries."	Updated to reflect the current study regions
5.1 Inclusion Criteria	4. added "with" before *NRS score*	To make it clearer for understanding
5.2 Exclusion Criteria	20. Changed from "~~Subject is, at the time of signing informed consent, a user of recreational or illicit drugs or has had a recent history (within the last year) (e.g., positive urine drug screening result) of drug or alcohol abuse or dependence.~~" to "Subject has a positive result on the screening urine drug screen and/or has had a history of drug or alcohol abuse or dependence within the last year"	Rephased sentence to avoid misunderstanding

	26. Added "or" to *a*, in front of *aspartate aminotransferase* Changed "Hemoglobin <10~~m~~g/dL" to "Hemoglobin <10g/dL"	To avoid misunderstanding To correct to a typo
	29. Changed from "~~(for positive anti-HCV only)~~" to "(for positive or equivocal anti-HCV)"	Revised to reflect central lab classification for viral serology test
	32. Changed from "~~Subject has a medical history of psychiatric disorder at any time (e.g., depression, schizophrenia, bipolar disorder) or has a history of epilepsy.~~" to "Subject has a medical history of confirmed psychiatric disorder (e.g., major depression, post-traumatic stress disorder, schizophrenia, bipolar disorder), has a history of epilepsy or has suicidal attempt, for whom it would not be recommended to stop concurrent medication therapy or may require medication that prohibited during study participation (refer to Section 6.5.2 and 10.5 for prohibited medication and washout period)"	To clarify and specify the definition of psychiatric disorder.
6.5.2 Prohibited Medications	Added "Medications that covered by urine drug screen (if applicable)" to table 6-4 Added "If there are medications not listed in the table above that need further clarification, consult the Hope Medicine Medical Monitor for suggestions." at the end of the section	To exclude the relevant medications that may impact pain evaluation from study participation Added an instruction to investigators for the relevant situation
7.1 Discontinuation of IMP	Changed "the subject will remain in the study until ~~**EOT**~~ visit" to "…… until **Visit 10**" Changed "should attend all subsequent visits up to ~~Visit **9**~~" to "should attend all subsequent visits up to **Visit 10 and complete all procedures (except IMP administration related) as outlined in the SoA**."	Updated follow-up period for subjects who discontinued from IMP, collecting safety information during a period that could cover 5 half-lives of HMI-115, further ensure subjects safety.

7.2 Subject Withdrawal from the Study	Changed from "~~In the event of withdrawn from the study during the treatment period, if possible, an early discontinuation visit (same as Visit 9)should be conducted (refer to Section 1.3)~~." to "In the event of withdrawn from the study during the treatment period, if possible, an early discontinuation visit (procedures same as Visit 9) needs to be performed as soon as possible and an on-site follow-up visit (procedures same as Visit 10) after 12 weeks from the last dose should be conducted. If the subject is unwilling to attend the on-site follow-up visit, a phone call follow-up should be attempted if the subject agrees, to collect safety information (monitoring AE, pregnancy status, concomitant medications) (refer to Section 1.3)." Added " In the event of withdrawn from the study during the follow-up period, if possible, an on-site follow-up visit (procedures same as Visit 10) is recommended to complete as soon as possible followed by a phone call follow-up at 12 weeks from the last dose to collect safety information (monitoring AE, pregnancy status, concomitant medications). If the subject is unwilling to attend an on-site follow-up visit, a phone call follow-up at 12 weeks from the last dose should be attempted if the subject agrees (refer to Section 1.3)."	Updated follow-up period for subjects who withdraw from study, collecting safety information during a period that could cover 5 half-lives of HMI-115, further ensure subjects safety.
	Added "and ADA" after "no additional PK"	To specify no additional sampling other than regular visits are required for those who discontinued from IMP
8.1.1 Electronic-Diary (e-Diary)	Added "Subjects need to return the e-diary devices after the completion of	Added an instruction for when to recall the device

	study participation or after withdrawal from the study."	
8.2.7 Dual Energy X-ray Absorptiometry (DXA)	Added "The window period for EOT visit, post-treatment month 6 and month 12 DXA scan is ±14 days."	To clarify the time window
8.4.1 Time Period and Frequency for Collecting AE and SAE Information	Changed "All AEs and SAEs will be collected from the signing of ICF until ~~the follow-up visit"~~ to "…… until **the end of study participation**"	This requirement also includes those who withdraw from study. Change the wording to avoid misunderstanding
8.4.3 Follow-up of AEs and SAEs	Changed "All SAEs" to "All **AEs and** SAEs"	To clarify all AEs will be followed not just SAEs
8.4.5 Pregnancy	Changed "~~Details of all pregnancies in subjects will be collected after the start of study intervention until the follow-up visit or at EOT visit (in case of premature discontinuation of IMP)~~." to "Details of all pregnancies in subjects will be collected from signing of ICF until the end of study participation"	Updated follow-up period for subjects who withdraw from study, collecting safety information during a period that could cover 5 half-lives of HMI-115, further ensure subjects safety.
8.10 Immunogenicity Assessments	Added "with one additional sampling point at week 17. All samples for ADA should be collected together with the corresponding PK sample." to the first paragraph	To clarify the ADA sampling time
8.11 Composite Pelvic Signs and Symptoms Score (CPSSS)	Added "e-Diary data or" Infront of *CPSSS Section 1*	To add an instruction
9.4.4 Primary Efficacy Endpoints and 9.4.5 Secondary Efficacy Endpoints	change from MMRM to ANCOVA as the primary analysis method	To make it more appropriate for the analysis of efficacy endpoints
9.4.8 Exploratory Analyses	Deleted "PK data will be compared ~~graphically and statistically"~~ Added "and Neutralizing antibody (NABs) will be summarized descriptively for each group at each visit." *to Anti-drug antibody (ADA)*	Specific method will be described in SAP Completed the analysis items

10.1.8 Source Documents	Added "e-Dairy source data will come from electronic device and be interfaced into EDC" in the end of this section	To clarify data source for e-Dairy
10.2 Appendix 2: Clinical Laboratory Tests	Added "within 7 days" to SARS-CoV-2 RT-PCR in front of *prior to randomization*	To clarify the testing time point
	Added "※Samples of coagulation test should avoid menstrual period."	Added an instruction for coagulation blood sampling
	Added "PRL" in front *PK and ADA*	PRL will not provide to investigator because of the potential risk for unblinding
	Added "High-dose biotin supplements (e.g., Vitamin B7 or H and coenzyme R and multivitamins) ingestion may interfere with some of the above laboratory tests and should be avoided at least 72 hours prior to blood collections."	Added requirement to avoid influence on lab tests
10.3.1 Definition of AE	Added "In clinical studies, an AE can include an undesirable medical condition occurring at any time, including screening or follow-up periods, even if no study intervention has been administered."	To clarify the record period of AE
10.3.3 Recording and Follow up of AE and SAE	Added "During the course of the study" in front of new or updated information will be recorded in the originally completed eCRF Added "Any AEs that are unresolved at last visit in the study are followed up by the Investigator for as long as medically indicated but without further recording in eCRF. For any patient with ongoing AE(s)/SAE(s) at the end of the study, the Sponsor retains the right to request additional information if judged necessary."	Added details to clarify how AEs should be followed

10.4 Appendix 4: Contraceptive Guidance	Added "or Phexxi" to spermicide Changed "double barrier" to "two forms"	To cover more choices To correct the definition
Version 1.0 to Version 2.0		
1.1 Synopsis Overall Design 4.1 Overall Design	Adjusted screening period from 45 days to 75 days. Added *"screening visit 2 (at least 35 days before V3 to ensure at least 5 weeks baseline pain score obtained before randomization)"* Remove "Baseline pain scores collection (5 weeks)" Change PK collecting time from "Day1 to ~~*Day 141*~~" to "Day 1 to *Day 169*"	To cover 2 complete menstrual cycles (21-35 days for a cycle) to give all subjects adequate time to complete the procedures in screening period, including 5 weeks baseline pain score obtained. To keep consistent with amended PK sample timepoint.
1.3 SOA Table 1-1 and Table 1-2	Adapted the SOA table for the rearranged procedures. Add "screening V2" and remove "baseline V2-V4" in version 1.0 All amendment per protocol relevant to the SOA table is revised accordingly	Since screening period extend to 75 days, to make operation feasible and convenience for subjects screening, visit frequency and relevant test are revised accordingly.
1.3 SOA Table 1-4 and Table 1-6	Added "Day1 pre-dose" sampling timepoint to sparse PK sub-group;	Correct an omission
1.3 SOA Table 1-3 to 1-6	Added "Week 25, Day 169" to intensive and sparse PK sampling schedules	To determine HMI-115 fully elimination and understand if

		PRL levels return to baseline when HMI-115 fully eliminated.
2.3.1 Risk Assessment Table 2-1	Revises the mitigation strategy of "clinical risk immune function" to "Careful monitoring of subjects for any ongoing, subclinical ~~disease~~ *infection* and exclusion of patients with existing ~~infection~~ *immunosuppression*".	Clarify and specify to monitor "infection" and exclude subjects with existing immunosuppression.
	Clinical risk of "PRLR blockage may induce PRL over section": Revised to "Increased PRL may cause disorder in the secretion of other sex hormones and *dopamine* and further induce conditions such as galactorrhea, change in menstrual cycles with oligo- or amenorrhea, hirsutism, acne, *change in mood*, etc. *However, considering the blockade of PRLR by HMI-115, the above conditions are very unlikely to be induced by HMI-115.* Collect galactorrhea, change in menstrual cycles with oligo- or amenorrhea, Hirsutism, Acne, *change in mood, etc., as adverse event of special interests (AESIs). Refer to Section 10.3.1*.	Add as supplemental instruction for PRLR blockade outcome. Theoretically, PRLR blockage will increase PRL and further may increase dopamine, however PRLR already has been blocked. All listed potential risks are more conceptional but need to monitor during study period.
	"Non-Clinical Risk- Bone cell metabolism, mitigation strategy": modified to *"Monitoring by CTX,*	Monitor biomarkers of bone formation/resorption to supplementally assess impact of

	P1NP, BSAP and DXA scan. Refer to Section 8.2.7 for details on DXA scan."	bone cell metabolism on top of BMD examination by DXA. No BMD impact had been demonstrated by 26 weeks toxicity study in cynomolgus monkey. Added biomarker plus DXA will provide evidence of no bone metabolism impact by HMI-115.
2.3.1.1 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Risk Assessment for COVID-19 Pandemic	Confirmation of COVID-19 infection by optional laboratory assessment will be conducted based on ~~availability (test capacity and turnaround time) of approved tests and on~~ Investigator's discretion *and/or local requirements and/or policy* *The measures may be adjusted according to local laws and/or policy*.	Considering COVID-19 complex and dynamic management policy among different countries and regions, investigators should follow local requirement and policy.
4.1 Overall Design	Delete "conduct at selected sites" for intensive PK subjects' selection	The subjects in intensive PK subset will be subjects who consent to perform intensive PK from any study sites.
	An e-Diary will be dispensed, and training will be provided to subjects at the ~~baseline Visit (~~Visit 2~~)~~ on how to record endometriosis-associated pain, uterine bleeding, and ~~analgesic~~ *rescue* medication use for endometriosis-associated pain on a daily basis	The baseline visits were designed in Protocol version 1.0 has been removed and replaced by screening visit 2, all relevant information revised accordingly. Rescue analgesic medication will be dispensed at Visit 2, clarify it is rescue medication to be recorded in diary, not all

		analgesic for pain other than endometriosis-associated.
5.1 inclusion criteria	Inclusion criterion #5: add note "subject with BI-RADS Classification 1 – 3 is eligible for randomization"	To specify normal results accepted for enrollment
	Deleted original #6 "Subject has not used hormonal therapies or medications associated with bone loss within the required time periods as per Section10.5." Integrated it with exclusion criterion #24 Subject has used medications such as hormones, analgesics, *medications associated with bone loss,* products that affect PRL levels, etc. within specific time window before Screening (refer to Section 10.5).	To make criteria simpler for reading
	Change #7 to "Subject agrees to use required (nonhormonal) birth control methods during the entire length of participation in the study (refer to Section 10.4) *and agrees to avoid pregnancy from signing the consent until 3 months after the last dose of IMP*"	Give timeframe for pregnancy prohibition after treatment discontinuation
5.2 exclusion criteria	Revised #8, remove endometrial biopsy *Subject* has clinically significant gynecologic condition ~~identified on~~	Endometrioma belongs to endometriosis and the size can vary along with menstrual cycle. It could be at the investigators' discretion to eliminate subjects

	~~Screening TVU or endometrial biopsy~~ other than endometriosis, ~~(~~including but not limited to: ~~complex ovarian~~ a. ~~cyst >3 cm or simple~~ ovarian cyst >5 cm (*except confirmed endometrioma*) that persists on repeat TVU; ~~clinically significant endometrial pathology; or~~ b. single fibroid ⩾ 4 cm or multiple [> 4] fibroids that measure ⩾ 2 cm ~~OR~~ *or* symptomatic submucosal fibroid of any size *on screening TVU* *c. Any ovarian tumors or pelvic masses of unclear etiology requiring further diagnostic procedures* *d.* acute or chronic endometritis.	with endometrioma of any size based on safety concerns. Endometrial biopsy is invasive.HMI-115 does not show any potential in increasing the risk in the development of endometrium malignancy from its MOA and previous studies data. It is also very unlikely that endometrial pathology will be deteriorated during short study period. If the subject has significant abnormality with their endometrium, there would be signs or symptoms and such abnormality could be detected through TVU. The subjects can seek for medical help whenever they find anything abnormal during the study period. Any ovarian tumors or pelvic masses of unclear etiology requiring further diagnostic procedures should be excluded.
	Revised #13 and #14 *Subject* has known any history of anterior pituitary, *posterior pituitary or hypothalamic* dysfunction, including but not limited to ~~hyperprolactinemia~~ *prolactinomas, hypogonadism, growth hormone deficiency*.	Adopted the U.S. FDA suggestions

	Subject has a current history of thyroid dysfunction (hyper-, or hypothyroidism)~~, hypogonadism, growth hormone deficiency~~.	
	Deleted original #16 “Subjects has family history of breast cancer or known breast cancer susceptibility gene (BRCA) mutation in her first-degree relatives.”	HMI-115 doesn’t have the potential to increase the risk of breast cancer based on the MOA and pre-clinical studies data. Measures have been taken to exclude subject with exist breast tumor from study including breast examination, and mammography for aged 40 and over.
	Removed “family history of prolactinomas” in #17	Prolactinoma is not an inherited disorder, and it has been moved to integrate with #13
	Added “(e.g., positive urine drug screening result)” to #20	To help with the judgement of drug abuse
	Changed DBP in #21 from > 95 mmHg to > 99 mmHg	We used the lower limit for stage II hypertension (SBP≥ 160mmHg and/or DBP≥100 mmHg) from "*hypertension Prevention and Cure Guideline of China*" as the reference to define subjects with uncontrolled hypertension.
	Chang ALT/AST requirement from ≥150% to ≥200% in #26a.	To keep consistent among HMI-115 clinical programs.

	Deleted “white blood cell count < 2500 mm3” in #26b	
	Changed “Papanicolaou test” to “cervical cytology” in #27	Provided more choices for different sites to perform this test in case Pap is not available in some sites.
	Modified #34 Subject has a history of osteoporosis or other metabolic bone disease, *or including any one or more of the following:* *a.* Low bone mass (Z-score ⩽ -2.0 on screening DXA scan [lumbar spine, femoral neck or total hip BMD]) OR *b.* *Body weight greater than 300 pounds or 136 kilograms (due to limits of DXA scanners) or* ~~Subject has~~ any condition that would interfere with obtaining adequate DXA measurements (e.g., history of spinal surgery, ~~spinal~~ hardware, severe scoliosis) or *artifact overlying the region of interest, including umbilical ring with refusal to remove*) *c.* History of fragility fracture OR *d.* History or presence of an unstable condition that is associated with a decrease in BMD (e.g.,	Adopted the suggestions from the U.S. FDA. to ensure the availability and reliable of DXA result.

	~~uncontrolled hyperthyroidism,~~ uncontrolled hyperparathyroidism, anorexia nervosa)	
	Added "Procedures that allowed to be repeated are listed in section 10.10" in the end of exclusion criteria section	To remind the investigators that some procedures could be repeated to enhance the possibility of subject recruitment.
6.1 Study Intervention(s) Administered	Added instructions of IMP administration under table 6-2	To guide the injection of IMP to mitigate injection site reactions
6.2 Preparation, Handling, Storage, and Accountability	Changed storage time from 6 hours to 4 hours.	Because microbial growth has in some cases been detected by 4 hours at 2-8°C following preparation for administration
6.5.2 Prohibited Medications	Added "*If a hormonal emergency contraception is used, the use of the drug and any associated menstrual cycle irregularity after the use should be documented*" under table 6-4.	Adopted the suggestions from the U.S. FDA
7 Discontinuation of IMP and Subject Withdrawal	Reordered the contents in this section. Adjusted the study pauses for safety reason (refer to section 7.3)	To make it easier to read and understand. Adopted the suggestions from the U.S. FDA
8.1.4 Endometriosis Daily Impact Pain Scale	Added "(last calendar day)" to last 24 hours	Add as a supplemental instruction

8.2.1 Physical Examinations	Adjusted the visit numbers for physical examinations Visit 1, Visit ~~5~~*3*, Visit ~~8~~*6*, Visit ~~11~~*9* and Visit ~~12~~*10*	Adjusted according to the adjusted overall procedures
8.2.3 Pelvic examination	Newly add section	To specify the pelvic examination to be operated and recorded by investigators
8.2.6 Transvaginal Ultrasound (TVU) Assessments	Change from "Significant ovarian findings on TVU include complex ovarian cyst > 3 cm or simple ovarian cyst > 5 cm. For the purposes of this study, an ovarian cyst whose appearance is consistent with an endometrioma will be considered to be complex" to "*The Screening TVU may be repeated per protocol (e.g., ovarian cyst criteria) or as clinically appropriate. An unscheduled (elective) TVU may also be performed as clinically indicated for subject evaluation during the course of the study*".	Modified according to update in eligibility criteria section
8.2.7 Dual energy X-ray absorptiometry （DXA）	Adjusted monitoring criteria and procedure for DXA Added "Subjects who prematurely discontinue treatment prior to week 11 will not have a DXA at the EOT visit or in the Post-treatment Follow-up Period"	Adopt the suggestions from the U.S. FDA HMI-115 is unlikely to induce bone loss from its MOA and previous studies data. Treatment less than 3 months is very short and unlikely to detect any changes through DXA.

8.11 CPSSS	Delete “from a 28 day recall period”	To make it more flexible to cover longer menses cycle (for instance 35 days)
9.3.1 Variables for Stratification of Randomization	This study employs a stratified randomization with~~region (China, United States) being the only~~ *two stratification* factors: *1) region 2) participation in the intensive PK sampling subset (Yes, No).* These stratification factors will be taken into account in the statistical analyses.	Add stratum of intensive PK to ensure subject in this subset will be well distributed by treatment arm.
9.4.3 Primary Efficacy Endpoints	Added “*The time frame for a visit for which the rescue medication use will be attributed to is defined as 5 weeks (35 calendar days) preceding the visit.*”	To clarify the timeframe of rescue medication information to be collected for analysis
9.4.7.7 DXA scan	Change “bone marrow density” to “bone mineral density”	Corrected a typo
10.1.5 Committees Structure	Changed DMC members to “*two unblinded experts in the fields of gynecology and one independent unblind biostatistician”. Details see DMC charter*. Remove “The DMC meeting will also include an unblinded Sponsor clinician and an unblinded Sponsor statistician. Unblinded Sponsor representatives will be independent of the study, and study personnel will remain blinded”.	To make committee member as odd for voting and easy to make conclusion

10.2 Appendix 2: Clinical Laboratory Tests	Adjusted the contents and some sampling requirements: Add "*CTX, P1NP and BSAP (exploratory)*" Add instruction that testing for COVID-19 should follow local requirement	Adjusted according to other parts in the protocol
10.3.1 Definition of AE	Combined original 10.3.3 AESI to this part and give specific instruction.	Adopted the suggestions from the U.S. FDA
	Added "Symptoms of dopamine withdrawal"	Adopted the suggestions from the U.S.FDA
10.3.4 Reporting of SAE	Change from 10.3.5 to 10.3.4 Deleted contacts which will be present in study safety management plan.	To make operation flexible, revised PV contact information as it may be updated during study ongoing and different by country.
10.4 Appendix 4	Delete "and Collection of Pregnancy Information" from the headline	The corresponding contents are in section 8.4.5
	Add "Subjects should avoid pregnancy from signing the consent until the completion of the study or 3 months after the last dose of IMP, whichever is longer." Change descriptions on urine pregnancy testing: Study subjects should only be included after a negative serum pregnancy test at Visit 1 *and a negative urine pregnancy at Visit 3.*	Clarify the timeframe that the subjects should avoid being pregnant Ensure pregnancy test can be well performed and well documented at site level.

	Urine pregnancy testing to be done ~~monthly thereafter~~ *at Visit 3, 5, 7, 9 and 10 through home pregnancy test kit. It will be under the supervision of investigators and the results will be recorded in source documents, then collected in EDC.*	
10.5 Appendix 5: Washout Intervals	Add "*Note: The drugs above should not be withdrawn by the investigator if used for treatment purposes, but rather the washout period may be used if the prescriber recommends discontinuation of any of these drugs*"	Adopted the suggestions from the U.S. FDA
10.10 Appendix 10	Newly added "Procedures that allowed to be repeated during screening period"	Specified the procedures that could be repeated for screening and made it more convenient for the investigators to refer