TITLE PAGE

Protocol Title:

A Phase 2a/b, Randomized, Double-blind, Placebo-controlled, Parallel Group, Multicenter, Clinical Study to Evaluate the Efficacy and Safety of OG-6219 in 3 Dose Levels, in Women 18 to 49 Years of Age with Moderate to Severe Endometriosis-related Pain

Protocol Number: OG-6219-P001

Amendment Number: 06

Compound: OG-6219

Brief Title:

A study to investigate efficacy and safety of OG-6219 BID in 3 dose levels compared with Placebo in participants aged 18 to 49 with moderate to severe endometriosis-related pain

Study Phase: Phase 2a/b

Sponsor Name: Organon LLC, a subsidiary of Organon and Co.

Legal Registered Address:

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Regulatory Agency Identifier Number(s): IND Number – 154574

EU-CTR Number: 2022-501310-57-00

Approval Date: 16 February 2024

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Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly.

This document is signed electronically. See the last page of the protocol for Sponsor signature

PPD

Executive Director Clinical Research

Date

Investigator Agreement Page is provided in Appendix 11. The Investigator should retain the original in the study site study files and return a copy to the Sponsor or Contract Research Organization for archiving.

Each Investigator should be sent a copy of the Investigator Agreement Page for completion. Signatures are obtained after the Sponsor has finalized and approved the protocol.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY

Document	Date	Region
Amendment 06	[16-Feb-2024]	Global
Amendment 05	[07-Nov-2023]	Global
Amendment 04	[16-Jun-2023]	Global
Amendment 03	[10-Feb-2023]	Global
Amendment 02	[03-Jan-2023]	Global
Amendment 01	[16-Sep-2022]	Global
Original Protocol	[17-Jun-2022]	

Amendment 06 (16-Feb-2024)

Overall Rationale for the Amendment:

The protocol OG6219-P001-06 has been amended to omit the interim analysis CCI [redacted]. At the originally planned timepoint for the described interim analysis (CCI [redacted]) it is currently projected that all participants would be enrolled and randomized to treatment. Because the duration of time it will take to stop the study enrollment at this timepoint, the planned interim analysis CCI [redacted] is no longer relevant.

Section number and Change	Description of Change (the information added is shown in bold, and deleted information is shown as a strike-out)	Brief Rationale
Section 1.1 Synopsis; Section 1.2 Study Schema; Section 2.3.1; Section 2.3.1 Risk Assessment; Section 2.3.3 Overall Benefit Risk Conclusion; Section 4.1 Overall Design; Section 7.3 Criteria for Study Termination; Section 9.3 Sample Size Considerations; Section 9.4.1 General Considerations; Section 9.5 Interim Analysis; Appendix 2: Regulatory, Ethical, and Study Oversight Considerations	Removed interim analysis (IA) CCI .	From a timing perspective the planned IA CCI is no longer relevant as it projected that all participants would have been enrolled and randomized by the planned IA timepoint. Clarification for psychometric analysis.
Section 5.2 Exclusion Criteria	Exclusion criteria #9 Has **a** ~~**no**~~ history of malignancy (except basal cell or squamous cell skin cancer) before signing informed consent.	Clarification that this is an exclusion criterion.
Appendix 3 Clinical Laboratory Tests	Table 9 Protocol Required Safety Laboratory Tests Removed Hemosiderin analyte from urinalysis	CCI

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:
A Phase 2a/b, Randomized, Double-blind, Placebo-controlled, Parallel Group, Multicenter, Clinical Study to Evaluate the Efficacy and Safety of OG-6219 in 3 Dose Levels, in Women 18 to 49 Years of Age with Moderate to Severe Endometriosis-Related Pain

Registry ID IND Number – 154574
EU-CTR Number: 2022-501310-57-00

Rationale:

Current medical treatments for endometriosis-related pain (ERP) are sometimes inadequate and have safety and tolerability issues that can limit their use, often leading patients to have repeated surgical interventions. Therefore, there is a need for development of new ERP medical therapies. A local inhibition of estrogen production at the ectopic implants level, for treatment of ERP, such as OG-6219, a novel inhibitor of hydroxysteroid-17β-dehydrogenase type 1 (HSD17β1), can potentially avoid the limitations and systemic liabilities of the current hormonal treatments.

The purpose of this global Phase 2a/b study is to determine the efficacy, safety, and tolerability of 3 dose levels of OG-6219 (CCI twice a day [BID]) in pre-menopausal women between 18 and 49 years of age (inclusive), who have moderate to severe ERP. The primary efficacy endpoint will assess the efficacy of 3 dose levels of OG-6219 in change from Baseline Cycle (BC) in endometriosis-related overall pelvic pain (OPP) score (the weighted mean of the dysmenorrhea [DYS] pelvic pain score and the non-menstrual pelvic pain score [NMPP; pain associated with micturition, defecation, ovulation, intercourse]) during the Treatment Cycle 3 (TRC3) compared to Placebo. The secondary endpoints will assess the efficacy of OG-6219 utilizing the DYS score versus Placebo at BC versus TRC3, and the NMPP score in addition to dyspareunia at BC versus TRC3. The study will also collect data health-related quality of life (HRQoL) using the 30-item Endometriosis Health Profile (EHP-30). The pain score entered CCI by each participant in the electronic diary (eDiary) must capture the worst pelvic pain (peak pain) corresponding to that day and should be entered at about the same time (before going to bed). Participants will make CCI entries regarding the severity of their OPP, DYS, NMPP into the eDiary to capture the efficacy endpoints of interest. In addition, data on the pharmacokinetics (PK) of OG-6219 and its primary metabolite FOR-1011 will be collected. Evaluation of efficacy will be based on the mean OPP, DYS, and NMPP scores collected using an eDiary. Safety and tolerability are primary objectives; the endpoint includes adverse events (AE), serious adverse events (SAE), laboratory assessments, assessment of electrocardiograms (ECGs), vital signs, physical exams, effect on systemic

hormones, effect on bone, effect on endometrium based on transvaginal ultrasound and endometrial histology, and assessments using the mental health evaluation via the Columbia-Suicide Severity Rating Scale (C-SSRS).

Objectives and Endpoints:

Objectives	Endpoints
Primary Endpoints The following primary efficacy endpoint will be assessed comparing Group A (CCI BID), B (CCI BID), C (CCI BID) with Group D (Placebo)	
• To evaluate the efficacy of 3 dose levels of OG-6219 (Group A, B, C) versus Placebo (Group D) in reducing OPP during TRC3, as measured by a NRS in the eDiary	• Change from BC to TRC3 in the mean OPP score[a]
The following primary safety endpoints will be assessed for Group A (CCI BID), B (CCI BID), C (CCI BID) and Group D (Placebo)	
• To evaluate the safety and tolerability of OG-6219	• Proportion of participants who experienced any AEs/SAEs • Abnormalities in clinical laboratory assessments, vital signs, and physical examination • Proportion of participants who prematurely discontinued study treatment due to AEs/SAEs
Secondary Efficacy Endpoints	
The following secondary endpoints will be assessed comparing Group A (CCI BID), B (CCI BID), C (CCI BID) with Group D (Placebo)	
1. To evaluate the efficacy of 3 dose levels of OG-6219 (Groups A, B, C) versus Placebo (Group D) in reducing DYS during TRC3, as measured by a NRS in the eDiary	• Change from BC to TRC3 the mean DYS score
2. To evaluate the efficacy of 3 dose levels of OG-6219 (Groups A, B, C) versus Placebo (Group D) in reducing NMPP during TRC3, as measured by a NRS in the eDiary	• Change from BC to TRC3 the mean NMPP score
3. To evaluate the efficacy of 3 dose levels of OG-6219 (Group A, B, C) versus Placebo (Group D) reducing dyspareunia during TRC3, as measured by a NRS in the eDiary	• Change from BC to TRC3 in the mean dyspareunia score
4. To evaluate the daily use of Sponsor provided rescue medication taken for ERP at TRC1, TRC2, and TRC3	• Change from BC to TRC1, TRC2, and TRC3 in the mean number of tablets of rescue medication for ERP • Change from BC to TRC1, TRC2, and TRC3 in the proportion of days participant has used rescue medication for ERP

Objectives	Endpoints
5. To evaluate the change in the PGI-S Score at different time points	• Change in PGI-S Score from C to CCI
6. To evaluate the change in the PGI-C Score in different time points	• Percentage of participants with any improvement on the PGI-C at TRC1, TRC2, and TRC3
7. To evaluate the change in the EHP-30 domains CCI from BC to TRC3	• Change from BC to TRC3 in the EHP-30 Domain Scores
Secondary Safety Endpoints	
8. To assess the incidence of clinically significant[d] changes from V1 to C in bone biomarkers: ○ CCI ○	• Mean change from V1 to C in bone biomarker levels
9. To assess the incidence of any clinically significant[d] changes in laboratory parameters from V1 to CCI	• Proportion of participants with clinical parameters of significance from V1 to CC I
10. To assess vaginal bleeding pattern over the 3 menstrual cycles (TRC1, TRC2, and TRC3) as captured in the eDiary	• Mean change from BC to TRC1, TRC2, TRC3 in the percentage of days with vaginal bleeding
11. To assess any potential change in the ECG parameters at CCI	• ECG parameter changes at CCI
Secondary PD / PK Endpoints	
12. To assess the change from V1 to C in serum hormone[b] concentrations	• Mean change from V1 to C in serum hormone levels
13. To assess any difference in serum hormone[b] concentrations at C between active treatment versus placebo	• Serum hormone levels comparing Group A (CCI BID), B (CCI BID), C (CC I BID) with Group D (Placebo)
14. To assess any difference in serum hormone[b] concentrations at C between active treatment versus placebo	• Serum hormone levels at C comparing Group A (CCI BID), B (CCI BID), C (CCI BID) with Group D (Placebo)
15. To assess the PK of orally administered OG-6219 and the active metabolite FOR-1011 using sparse and intensive[c] PK sampling.	• Plasma concentrations of OG-6219 and FOR-1011 at scheduled assessments using sparse PK sampling during the treatment period. • C_{max}, T_{max}, and AUC_{tau} for both OG-6219 and FOR-1011 on CCI for the population with intensive PK sampling
CCI	

CCI

Note: Refer below and to Figure 1

- Screening Cycle is between C and C .
- Baseline Cycle is defined as CCI which starts at C (first day of the menses) and ends at one-day before next menses.
- Treatment Cycle 1 is the period between the first day of menses associated with treatment start (C) to the day prior to the first day of next menses, regardless of number of days.
- Treatment Cycle 2 is the period between the first day of second menses after end of BC to the day prior to first day of next menses, regardless of number of days.
- Treatment Cycle 3 or EOT is the period between the first day of third menses after end of BC to either end after CCI on study treatment, whichever occurs first.
- Safety Follow-up Cycle is the period time between the first day after stopping study treatment during TRC3 and ends after 30 consecutive days.

a. OPP score is defined as the combination of the DYS and NMPP scores in a cycle
b. CCI
c. Intensive PK sampling is optional and applicable for subset of PK analysis set, where a separate consent would be provided.
d. Clinical significance is defined as any variation in physical findings or laboratory assessments that has medical relevance and may result in an alteration in medical care refer to Section 8.3.1 and Section 8.3.7.

Abbreviations:
AE=Adverse event;
CCI
BC=Baseline Cycle;
C-SSRS=Columbia-Suicide Severity Rating Scale;
CCI
DYS=Dysmenorrhea;

CCI
ECG=Electrocardiogram;
EHP-30=Endometriosis Health Profile-30;
CCI
CCI
NMPP=Non-menstrual pelvic pain;
CCI
PGI-S=Patient Global Impression of Severity;
SC=Screening Cycle;
CCI
TRC1=Treatment Cycle 1;
TRC3=Treatment Cycle 3;
V=Visit;
CCI
eDiary=Electronic diary;
EOT=End of Treatment;
ERP=Endometriosis-related pain;
NRS=Numeric rating scale;
OPP=Overall Pelvic Pain (endometriosis-related);
PGI-C=Patient Global Impression of Change;
PK=Pharmacokinetic;
CCI
TRC2=Treatment Cycle 2;
CCI

Overall Design:

This is a global multicenter, Phase 2a/b, randomized, double-blind, Placebo-controlled, 4-arm proof of concept, dose-range study to assess the efficacy, safety, and tolerability of 3 dose levels of OG-6219, in pre-menopausal women 18 to 49 years of age (inclusive), who have been surgically diagnosed with endometriosis within the last 4 months to 10 years prior to Visit 1 (V1) and with moderate to severe ERP.

The study duration of approximately 28 weeks includes: an initial period of approximately 2 to 4 weeks. between V1 and CCI to collect safety laboratory assessments. Each cycle refers to 1 menstrual cycle around 21 to 32-day duration. A Screening Cycle (SC), between CC and CCI ; A BC or Single-blind CCI , between CC and CCI . A Randomization Visit (CC), to treatment allocation with a ratio of CCI to 3 active arms and 1 Placebo arm. This is a double-blind treatment cycle across 3 menstrual cycles, Treatment Cycle 1 (TRC1), Treatment Cycle 2 (TRC2), and Treatment Cycle 3 (TRC3) or End of treatment (EOT); and is followed by a Safety Follow- up Cycle (SFC). Overall, the study includes C C on-site visits and C C phone contacts, as detailed below:

- Screening Period:
  - One SC: Starts at CC (first day of the menses) and ends one-day before next menses.
  - One BC during the single-blind, CCI period: Starts at CC (first day of the menses) and ends at one-day before next menses.
- Randomization: CC, this is on first day of the next menses after the end of BC.
- Treatment Period: Three treatment cycles (TRC1, TRC2, and TRC3) after CC:
  - TRC1 is the period between the first day of menses associated with treatment start (CC) to the day prior to the first day of next menses, regardless of number of days. CCI

- TRC2 is the period between the first day of second menses after end of BC to the day prior to first day of next menses, regardless of number of days. Phone Contact [redacted] is done during the menses.
- TRC3 or EOT is the period between the first day of third menses after end of BC to either end after [redacted] completed cycles or [redacted] on study treatment, whichever occurs first.

- Safety Follow-up:
  - SFC, is the period of time between the first day after stopping study treatment during TRC3 and ends after 30 consecutive days (regardless of whether it aligns with first day menses or not). Phone contact [redacted] is done at [redacted] after last intake of study treatment. [redacted] at the first day of next menses is considered End of Study (EOS).

At [redacted], participants will receive the eDiary which will be used [redacted] until the EOS ([redacted]) to collect the [redacted] (worst) pelvic pain scores (DYS, NMPP, dyspareunia). The pain score entered [redacted] by each participant in the eDiary must capture [redacted] corresponding to that day and should be entered at about the same time (before going to bed). The eDiary will also collect [redacted] as well as mental health assessment via C-SSRS will be collected according to the Schedule of Activities (SoA). Participants' safety will be continuously monitored by the Sponsor and by an external Data Monitoring Committee [DMC] committee throughout the study (at ongoing and pre-defined windows).

Number of Participants:

Approximately [redacted] pre-menopausal females aged 18 to 49 years old (inclusive), who have been surgically diagnosed with endometriosis within the last 4 months to 10 years prior to V1, will be screened to achieve 380 randomly assigned to study treatment ([redacted] participants per group). A minimum subset [redacted] per treatment group (including Placebo group) will be voluntarily enrolled for optional intensive PK sampling for the entire duration of the study.

Study Treatment Groups and Duration:

Treatment Arm	Treatment	Dose	Blinded Doses	Sample Size	Route of Administration	Regimen/ Treatment Period[a]	Use
CCI	OG-6219 CCI	CC BID	CCI BID (Bottle A) CCI BID (Bottle B)	N=C (minimum)	Oral	Single-blind Treatment Period CCI	CCI
OG-6219 CCI BID	OG-6219	CCI BID	CCI BID (Bottle A) CCI BID (Bottle B)	N=C	Oral	Double-blind Treatment Period CCI	Experimental
OG-6219 CCI BID	OG-6219	CCI BID	CCI BID (Bottle A) CCI BID (Bottle B)	N=C	Oral	Double-blind Treatment Period CCI	Experimental
OG-6219 CCI BID	OG-6219	CCI BID	CCI BID (Bottle A) CCI BID (Bottle B)	N=C	Oral	Double-blind Treatment Period CCI	Experimental
Placebo	OG-6219 Placebo	CC BID	CCI BID (Bottle A) CCI BID (Bottle B)	N=C	Oral	Double-blind Treatment Period CCI	Placebo

Abbreviations: BID=twice a day; V=visit.
[a] Maximum treatment duration must not exceed CCI

Statistical Methods:

Efficacy:

The primary endpoint will be the mean change from BC of the average daily OPP score during TRC3. The OPP will be calculated for each cycle as the total of OPP scores reported during the cycle divided by the number of days during the cycle in which the score was reported. For participants who discontinue early, their last cycle will be associated with the cycle number at entry into the cycle. The primary analysis will be conducted using all participants with a post-treatment OPP measurement and will use a longitudinal model. The response vector for the model will be change from BC in the average OPP during TRC1, TRC2, and TRC3. Model terms will include the respective baseline, treatment, time (ie, cycle), and treatment-time interaction, allowing for the inclusion of individual outcomes over time (cycle). An unstructured error structure will be assumed. If nonconvergence is encountered, compound symmetry (CS) and first-order autoregressive AR(1) error structures will be considered.

Least squares mean change from baseline for each treatment group, with corresponding standard errors will be provided. Estimated treatment differences (each active treatment group versus Placebo) with corresponding 95% confidence intervals and 2-sided p-values will also be provided for each active treatment group. No missing data will be imputed for the primary analysis.

Supportive analyses will be conducted using an analysis of covariance (ANCOVA) on the change from baseline to the TRC3, with treatment as a fixed factor and baseline OPP as a covariate.

Secondary endpoints assessing change in continuous endpoints over time (either measurements within the cycle or at an individual visit) will use longitudinal models as described for the primary endpoint and/or ANCOVA models. Changes from SC to SFC will be compared using ANCOVA models using all participants with an OPP measurement during SFC. Select longitudinal models which focus on TRC1 and TRC2 may exclude TRC3 from the model. An unstructured error structure will be assumed for all longitudinal models. If nonconvergence is encountered, CS and AR (1) error structures will be considered.

Primary Safety Analysis:

The proportions of participants who experienced the following will be summarized

- A treatment-emergent adverse event (TEAE)
- Premature discontinuation of study treatment due to an AE
- Changes from baseline to EOS abnormalities in clinical laboratory assessments, vital signs, and physical and gynecological examination

Pharmacokinetics:

- PK analysis set: The PK analysis set is a subset of the Safety analysis set (SAF) and will include all participants who received at least 1 dose of OG-6219 and have at least 1 quantifiable OG-6219 concentration.
- PK analysis set for noncompartmental analysis: The PK analysis set for noncompartmental analysis (NCA) will include all participants in the PK analysis set who chose intensive PK sampling in Day 1 (CC) and CC. Intensive PK sampling is optional where a separate consent would be provided.

OG-6219 and its primary metabolite FOR-1011 concentrations (all participants receiving OG-6219) will be summarized by treatment, study visit, and scheduled time for the PK analysis set, as appropriate.

Pharmacodynamics:

- PD analysis set: The pharmacodynamic (PD) analysis set is a subset of the SAF and will include all participants who received at least one dose of OG-6219 or Placebo and have at least 1 post-dose evaluable PD endpoint without protocol deviations or events affecting the PD results.

The PD and exploratory endpoints and change from baseline results will be summarized by treatment and scheduled time, where appropriate, for the PD analysis set.

Interim analysis (IA):

There will be no IA CCI . An interim psychometric analysis using blinded data will be performed to affirm methods for establishing pain responder cutoffs.

Data Monitoring/Other Committee: Yes

1.2 Schema

Figure 1 Study Schema

1.3 Schedule of Activities

Study Period	Screening	CCI	Randomization and Treatment Period	CCI	Safety Follow-up	CCI	Discontinuation
Window (days)	CCI						
Timing		Start of SC	Start of BC	Start of TRC1	CCI	Start of TRC2	Start of TRC3	Start of SFC	Day 14 after stopping intake of study medication	End of the SFC	
Informed Consent	X[b]										
Inclusion, Exclusion/Eligibility criteria	X	X	X	X[c]							
Demographics	X										
Medical History (includes current condition, eg, documentation of surgical diagnosis of endometriosis[d])	X										
Gynecological History	X										
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X

Study Period	Screening			Randomization and Treatment Period				CCI	Safety Follow-up		Discontinuation
CCI											
Window (days)	CCI										
Full Physical Examination (including height and weight)	X							X			X
Focused Physical Examination (Cardiac, Respiratory, GI)				X	X		X			X	
Gynecological Examination[e] / Contraception Counseling[f]	X							X		X	X
Rescue Medication Dispensing and Instructions for Use		X	X	X	X		X	X			
Home UPT Dispensing[g]	X		X	X							
Treatment Allocation				X							
CCI			X								
				X[h]	X[i]		X				
OG-6219/Placebo Accountability				X[h]	X		X	X			X
Dispense/Collect eDiary		X	X	X						X	X

Study Period	Screening			Randomization and Treatment Period				CCI	Safety Follow-up		Discontinuation
CCI		CCI							CCI		
Window (days)	CCI										
eDiary Training/Re-training[j]		X	X	X	X		X	X			
eDiary Compliance[k]			X	X	X	X	X	X	X	X	
eDiary CCI		←								→	
				■				■			
Patients' Impression of Change (PGI-C)[l]						X	X	X			
Patients' Impression of their Overall Severity (PGI-S)[l]				X		X	X	X			

Study Period	Screening			Randomization and Treatment Period				CCI	Safety Follow-up		Discontinuation
CCI	CCI								CCI		
Window (days)	CCI										
Vital Signs (Heart Rate, Blood Pressure, Respiratory Rate, Temperature)	X	X	X	X	X		X	X		X	X
12-Lead ECG	X			X[m]	X[m]		X[m]	X		X	X
Clinical Laboratory Tests (Hematology and Chemistry panels)[n]	X			X	X		X	X		X	X
Urinalysis	X			X	X		X	X		X	X
STI Panel[o]	X										
UPT[p]	X	X	X	X	X	X	X	X		X	X
Serum Pregnancy Test (β-hCG)[q]	X		X	X	X		X	X		X	X
CCI											
AE	X	X	X	X	X	X	X	X	X	X	X

Study Period	Screening			Randomization and Treatment Period				CCI	Safety Follow-up		Discontinuation
CCI											
Window (days)	CCI										
Plasma PK Sampling[u]											X
CCI											
Columbia-Suicide Severity Rating Scale (C-SSRS)[l, y]	X	X	X	X	X		X	X		X	X

Abbreviations: AE=Adverse event; BC=Baseline Cycle; CCI C-SSRS=Columbia-Suicide Severity Rating Scale; CCI DX=Day X; DYS=Dysmenorrhea; CCI ; ECG=Electrocardiogram; eDiary=electronic diary; EHP-30=Endometriosis Health Profile-30; EOS=End of Study; EOT=End of Treatment; CCI GI=Gastrointestinal; hCG=Human chorionic gonadotropin; HRQoL=Health-related quality of life; CCI ; NMPP=Non-menstrual pelvic pain; CCI OPP =Overall pelvic pain (endometriosis-related); PAP=Papanicolaou; CCI PGI-S=Patient Global Impression of Severity; PK=Pharmacokinetic; CCI PRO= Patient-reported outcome; SC=Screening Cycle; SFC=Safety Follow-up Cycle; CCI STI= Sexually transmitted infection; CCI

CCI TRC1=Treatment Cycle 1; TRC2=Treatment Cycle 2; TRC3=Treatment Cycle 3; CCI UPT=Urine pregnancy test; VX=Visit X; CCI ; ~ = approximately.

a. V1 is recommended to occur around bleeding day (menses).
b. Screening may occur over several days after informed consent is signed.
c. Recheck clinical status before randomization (CCI), and/or first dose of study treatment.
d. Surgical diagnosis of endometriosis is confirmed by documentation in the medical records.
e. Examination includes speculum insertion, bimanual examination, and breast examination. If a previous PAP smear report is available and the results meet the local guidelines, no additional tests are needed; otherwise, the PAP smear should be performed at Screening.
f. Post-study contraceptive counseling CCI ; Participants who do not wish to conceive CCI should begin a new contraceptive method as soon as possible. Post-study contraceptive counseling will be provided by study site personnel in accordance with the SoA.
g. The UPT is centrally provided. If any menstrual cycle delay is noted, the participant must immediately perform UPT and contact clinic to schedule a visit as soon as possible and the Sponsor must be contacted. Additional UPT can be dispensed as needed.
h. C Participant must be CCI compliant with CCI to be randomized.
i. A tablet count will be performed at C and open bottles returned to participants to complete Cycle 1 treatment.
j. Participants will begin daily CCI completion at C. Investigator or designees should explain the importance of completing the eDiary CC. Investigators are to evaluate participants compliance with the eDiary during screening to assess eligibility per inclusion criteria. Participants who are not complaint should be re-trained.
k. Participant compliance with eDiary entries must be CCI during both the SC and the BC to be randomized (information to be provided by the eDiary portal).
l. CCI
m. ECG will be performed pre-witness dose and 1.5 hours after dose (witness dose), following the PK Sparse assessment.
n. CCI
o. If indicated, participants will be tested for gonorrhea and chlamydia unless they were screened within the past 3 months and have no new sexual partner. Testing for trichomonas and bacterial vaginosis will only be required if abnormal vaginal discharge is present. Testing will be performed locally and may be repeated during the study as needed.
p. If local regulations indicate that UPT should be performed more frequently, follow local regulations where applicable.
q. In addition to visits specified, serum pregnancy test also required any time pregnancy is suspected or if UPT is positive (unless pregnancy already confirmed by ultrasound).

CCI

u. OG-6219 and active metabolite FOR-1011; blood samples for PK analysis will be collected at all visits during the dosing period including the EOT Visit and discontinuation. In addition, for the optional intensive PK sampling, a minimum of C participants per treatment group (incl. Placebo group) will be enrolled on CCI , for entire duration of the study. A complete schedule of PK assessment times is found in Table 8. The witness dose should be administered at site for CCI .

v. C sample collection to be collected within 12±4 hours of last dose of study medication. If not possible, the PK sample should be collected at C irrespective of the timing of the last study dose taken.

CCI

y. Based on determination of positive C-SSRS results for suicidality, the participants will be discontinued from the study medication and referred to a specialist at the Investigator's discretion for further evaluation. In addition, the positive results from C-SSRS evaluation will have to be treated as an SAE and reported to the Sponsor in a timely manner.

2.0 INTRODUCTION

Organon is developing OG-6219 (formally known as FOR-6219) for the treatment of moderate to severe endometriosis-related pain (ERP). Organon acquired Forendo on 13 December 2021 and is now the owner and developer of OG-6219 as a novel hydroxysteroid-17β-dehydrogenase type 1 (HSD17β1) enzyme inhibitor for the treatment of moderate to severe pain in endometriosis.

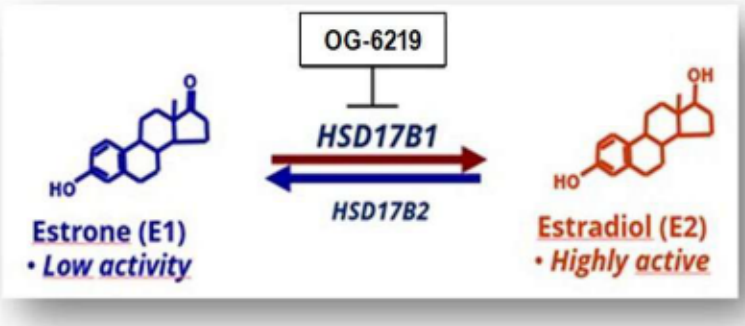
The main source of circulating estrogens in pre-menopausal women is the ovary. However, estrogens are also synthetized in peripheral tissues. Local biosynthesis of biologically active estradiol (E2) within the endometriotic lesions is thought to play a central role in the pathophysiology of endometriosis.[1-3] In general, only a very small proportion of E2 and the androgens (testosterone, and dihydrotestosterone [DHT]), produced intracellularly by the steroidogenic enzymes of the intracrine pathways diffuse into the circulation, thus avoiding systemic effects. This intratissue hormone metabolism is known as intracrinology or intratissue hormone metabolism and is considered an important part of the endocrine control at the end organ level.[4,5]

Hydroxysteroid-17β-dehydrogenases (HSD17βs) are a family of enzymes that catalyse the interconversion between the active and inactive forms of specific steroidal hormones on the final steps of their biosynthesis.[6-8] In mammals, there are at least 15 HSD17β1 enzymes and the nomenclature of these enzymes follow their discovery; the majority of these belong to the short-chain dehydrogenase/reductase (SDR) family.[9]

In the late 1980's, the human HSD17β1 was the first member of the HSD17β enzyme family to be cloned and sequenced.[9,10] Among the HSD17β enzymes, HSD17β1 possesses the highest specificity for steroids as a substrate and the highest catalytic activity for converting the low active estrone (E1) to highly active E2 (17β estradiol; E2) and is always involved in the final E1 to E2 activation step.[11,12] This occurs in target cells where the estrogenic effect is exerted via the estrogen receptor.

The hydroxysteroid-17β-dehydrogenase type 2 (HSD17β2) catalyzes the opposite reaction converting highly active E2 to the less active E1. Thus, HSD17β1 and HSD17β2 regulate the balance between the highly active E2 and less active E1, which has shown to be essential for the regulation of intratissue estrogen concentrations both in the endometrium and endometriosis lesions (implants).[1,13] (Figure 2).

Figure 2 HSD17β1 and HSD17β2 enzymes regulate the balance of the low active E1 and highly active E2 in endometriotic lesions



Abbreviations: HSD17B1=Hydroxysteroid-17β-dehydrogenase type 1; HSD17B2=Hydroxysteroid-17β-dehydrogenase type 2.

An imbalance between HSD17β1 and HSD17β2 in endometriotic lesions as compared to normal endometrium has been demonstrated.[2,14,15] This is attributed to the failure of upregulation of HSD17β2 in endometriotic lesions due to their functional progesterone resistance[16,17] and therefore contributing to the increased E2 levels, ie, more estrogenic environment in the endometriotic lesions.

HSD17β1 expression is seen in the eutopic endometrium throughout the cycle.[18] The HSD17β1 and HSD17β2 are both expressed in endometrium and endometriotic implants[20]; however, there is an imbalance between HSD17β1 and β2 in endometriotic lesions as compared to normal endometrium (eutopic endometrium).[2,14,15]

In a recently published study[21], in which protein levels of different enzymes were determined in both eutopic endometrium and endometriotic lesions, eutopic endometrium presented higher levels of aromatase, compared to steroid sulfatase (STS) or HSD17β1, while endometriotic lesions had superior levels of STS and HSD17β1.

The pharmacological action of the novel HSD17β1 enzyme inhibitor OG-6219, is based on its potent and selective binding to HSD17β1[22] and ability to inhibit E2 production from E1.[23,24] OG-6219 is not expected to interfere with the biological effects of circulating E2 because the putative mechanism of action is based on its ability to inhibit local conversion of E1 to E2 in endometriotic lesions without evidence of any off-target effects. Furthermore, OG-6219 has no intrinsic estrogenic or antiestrogenic activity, and no agonist or antagonistic activity at the progesterone receptor B. Screening in vitro for activity with 13 enzymes and 74 different binding assays further confirmed the absence of off-target effects with OG-6219.[25-27]

CCI

CCI [redacted]. As proof of concept (PoC), HSD17β1 inhibitors have demonstrated the ability to reduce the lesions size and number in a marmoset monkey endometriosis model[28] and inhibit the E2 formation in human endometriotic lesions ex vivo.[29] These data as well as other studies,[30,31] demonstrate the importance of the local E2 metabolism independent from the ovarian steroidogenesis and suggests HSD17β1 as a valid target for the treatment of ERP. An inhibitor of HSD17β1 should therefore be suitable in preventing the local synthesis of E2 in endometriotic lesions[2,15,20] and may have therapeutic activity in ERP.

2.1 Study Rationale

Current medical treatments for ERP are sometimes inadequate and have safety and tolerability issues (systemic effects) that limit their use, often leading patients to have repeated surgical interventions.[32] There is a compelling unmet medical need for a new medical therapy based on a local inhibition of estrogen production at the ectopic implants level (which could be shown in pre-clinical experiments), for treatment of ERP, such as OG-6219, a novel HSD17β1 enzyme inhibitor, which can avoid the limitations and systemic liabilities of the current hormonal treatment.

The purpose of this global Phase 2a/b study is to determine the efficacy, safety, and tolerability of 3 dose levels of OG-6219 (CCI [redacted] BID) in pre-menopausal women between 18 and 49 years of age (inclusive), who have been surgically diagnosed with endometriosis within the last 4 months to 10 years prior to Visit 1 (V1) and who have moderate to severe ERP. The primary efficacy endpoint will assess the efficacy of 3 dose levels of OG-6219 in change from Baseline Cycle (BC) in the OPP score (the mean of the dysmenorrhea [DYS] pelvic pain score combined with the mean of the non-menstrual pelvic pain [NMPP] score) during the Treatment Cycle 3 (TRC3) compared to Placebo. The secondary endpoints will assess the efficacy of OG-6219 utilizing the DYS score versus Placebo at BC versus TRC3, and the NMPP score in addition to dyspareunia at BC versus TRC3. CCI [redacted] The pain score entered CCI [redacted] by each participant in the electronic diary (eDiary) must capture the CCI [redacted] (peak pain) corresponding to CCI [redacted] and should be entered at about the same time (before going to bed). Participants will make CCI [redacted] entries regarding the severity of their OPP, DYS, and NMPP into the eDiary to capture the efficacy endpoints of interest. In addition, data on the pharmacokinetics (PK) of OG-6219 and its primary metabolite FOR-1011 will be collected. Evaluation of efficacy will be based on the mean OPP, DYS, and NMPP scores collected using an eDiary. Safety and tolerability is a primary objective; the endpoint includes adverse events (AE), serious adverse events (SAE), laboratory assessments, assessment of electrocardiogram (ECG), vital signs, physical exams, effect on systemic hormones, effect on bone, effect on endometrium based on transvaginal ultrasound (TUVS) and endometrial histology, and assessments using the mental health evaluation via the

Columbia-Suicide Severity Rating Scale (C-SSRS). Refer to the objective and endpoint (Table 1) for more details.

2.2 Background

Endometriosis is a chronic and often debilitating disease that affects up to 10% of women of reproductive age.[33] Endometriosis is defined by the presence of endometrium-like tissue outside the uterine cavity; definitive diagnosis is obtained through surgical visualization of lesions.[34] The main phenotypes that frequently coexist are superficial peritoneal lesions, deep infiltrating endometriosis, ovarian endometriotic cysts (endometriomas). The predominant clinical symptoms of endometriosis are DYS, chronic pelvic pain, pain during intercourse (dyspareunia), and infertility. Endometriosis-related pain can have a significant impact on patients' Quality of Life (QoL) and can result in a substantial economic burden.[35,36]

Definitive diagnosis for endometriosis is obtained through surgical visualization[34]; however, the most recent guidelines of the European Society of Human Reproduction and Embryology states that a diagnosis of endometriosis can also be based on a combination of clinical symptoms, imaging (magnetic resonance imaging [MRI] and/or ultrasound) and/or positive response to empiric treatment.[37]

Several factors have been suggested to be involved in the pathogenesis of endometriosis, including aberrant hormonal regulation, inflammation, as well as genetic and environmental factors.[3,34,38] Estrogen-driven inflammation is thought to be the central process that shapes the pathology of endometriosis[20,39] and is mediated by overproduction of inflammatory mediators such as cytokines, prostaglandins, and growth factors involving the innate and adaptive immune response system.[40,41] Chronic inflammation, resultant adhesions, and other factors contribute to the main clinical symptoms. Pain is thought to be caused by inflammatory mediators and also has a neurogenic component[41]. In chronic stages, central sensitization also plays an important role in ERP, by amplifying the pain signal from the periphery.[41]

Treatment consists of surgical removal of lesions and medical treatment (hormonal medication).[34] Medical therapy is often initiated without surgical confirmation of the disease, and a positive response can support the diagnosis.[37,38] Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to relieve DYS, although there is no clinical proof of efficacy in the management of ERP.[42] Combined oral contraceptives (COC) used off-label and progesterone, alone or in combination with pain medication (NSAIDs or opioids) are most widely used for long-term treatment, but side effects include the risk of myocardial infarction, stroke, or venous thromboembolism for COC[43,44] and irregular bleeding patterns, breast tenderness, and mood disturbances for progestins. Other hormonal therapies include gonadotropin releasing hormone (GnRH) agonists and antagonists may induce a severe hypoestrogenic state resulting in menopausal symptoms, progressive bone loss, hot flashes, vaginal dryness, decreased libido etc.[43,45] In addition to treatment cost, the GnRH agonists and high-dose GnRH antagonists are

therefore restricted for short-term use only, and low dose GnRH antagonists are limited to 2 years.[46] Hormonal add-back regimens are being used with GnRH agonists in order to prevent bone loss: These include progestins monotherapy such as norethisterone/norethindrone acetate, estrogen-progestin combinations, among other, and have showed some effects in lumbar, but not femoral bone loss.[47] Add-back therapy in combination with GnRH antagonists is currently being investigated.[45] In addition, aromatase inhibitors are sometimes used off-label in combination with oral contraceptives, progesterone, or GnRH agonists or antagonists, but their use is recommended only after all the other treatment options are exhausted, due to associated severe adverse effects.[37] Other hormonal therapies, ie, contraceptive ring or implant, transdermal (estrogen/progestin) patch, anti-progestogens (gestrinone), and levonorgestrel-releasing intrauterine system, are also mentioned as potential treatment options.[37]

The available treatment options provide symptom relief only and are not disease modifying; at present there is no cure for the condition. Hormonal treatment can alleviate ERP; however, for many women the pain relief is temporary and limited in efficacy, and the symptoms often reoccur after treatment discontinuation.[48,49] All present hormonal treatments for ERP also suppress the hypothalamic pituitary gonadal (HPG) axis; some require non-hormonal contraception or cannot be used with oral contraceptives. OG-6219 is a novel HSD17β1 enzyme inhibitor being developed for the treatment of moderate to severe ERP. The pharmacological action of OG-6219 is based on its potent and selective binding to HSD17β1 and ability to locally inhibit E2 production. Thus, there is a compelling, unmet medical need for a new, medical therapy potentially without systemic effects for treatment of ERP, such as an oral, potent, selective inhibitor of HSD17β1 which can avoid the systemic AE impact of hormonal treatments.

Alternative treatment options that are both effective and can be used long-term are warranted; there is a high medical need for new treatment options that are both effective and can be used long-term without modification of the HPG axis with the induction of a hypoestrogenic, hyperprogestagenic, or hyperandrogenic status with subsequent multiple systemic liabilities. OG-6219 is a novel HSD17β1 enzyme inhibitor being developed for the treatment of moderate to severe ERP. The pharmacological action of OG-6219 is based on its potent and selective binding to HSD17β1 and ability to locally inhibit E2 conversion from E1.

2.3 Benefit/Risk Assessment

The Sponsor will immediately notify the Principal Investigator if any additional safety or toxicology information becomes available during the study.

This study will be performed in compliance with the protocol, International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (GCP), European Union Clinical Trial Regulation (EU CTR) number 536/2014, and applicable regulatory requirements.

2.3.1 Risk Assessment

Two metabolites of OG-6219 were assessed for potency; the primary metabolite, FOR-1011, has the same low nanomolar potency for inhibition of human HSD17β1. A further metabolite, FOR-6287, is less potent than OG-6219. Both metabolites are formed in the animal species used for toxicological evaluation. The toxicity of OG-6219 has been evaluated in repeat oral dose studies with up to CCI duration in rats and monkeys with no adverse findings or treatment related deaths. In the CCI studies, the No Observed Adverse Effect Level was determined to be CCI, the highest dose level tested. Exposure was saturated in both species and the safety margins compared to human exposure at steady state at the highest clinical dose (CCI BID) were CCI for OG-6219 with the corresponding margin for FOR-6287 being in the range of CCI. FOR-1011 was only identified as the primary metabolite in the first-in-human study and was therefore quantified only in a limited number of studies. The safety margin for FOR-1011 was CCI in rats and CCI in monkeys.

OG-6219 was found to be safe and well-tolerated in Phase 1 with exposure of a total of 71 healthy, female participants, of which 37 participants were pre-menopausal (Part III); 10 pre-menopausal participants were treated with the highest dose of CCI BID for 14 days after the start of the menstrual cycle. The number of participants with treatment-emergent adverse events (TEAEs) in the safety analysis set, demonstrated a frequency of CCI in the active treatment versus the Placebo group of CCI. No serious AEs and no deaths were reported. None of the TEAEs were severe in nature. Overall, gastrointestinal disorders were the most frequently reported TEAEs CCI, with abdominal pain being reported most commonly CCI. CCI of participants who received active treatment at any dose reported a gastrointestinal TEAE, versus CCI of Placebo. The nervous system disorders were the next most common TEAE (reported at least once) where CCI in the active group at any dose level versus CCI of the Placebo group; headache being reported most frequently. All TEAEs were mild except 2 which were moderate, and both reported in the nervous system disorders (CCI); one was in active treatment group and one in the Placebo group.

No clinically relevant changes in ECG, vital signs, safety laboratory, CCI

In this Phase 2a/b 4-arm PoC, dose-range study, treatment over CCI is intended to assess the effect of treatment with OG-6219 on efficacy, safety, and tolerability over C menstrual cycles.

While a previous study in cynomolgus monkeys exposed to OG-6219 for a total of CCI did not find any statistically significant changes in the mean CCI . An increase CCI in this Phase 2a/b study, if any, is expected to be fully and quickly reversible.

CCI

Also, no macroscopic or microscopic effect on bone tissue was observed in the CCI toxicology studies in rat and cynomolgus monkeys. However, no clinical experience on the effect of OG-6219 on systemic estrogen levels with longer exposure is available.

CCI Effects on coagulation and lipid parameters as well as cardiovascular function will be monitored by serum chemistry, vital signs, and ECGs.

Participants will need to stop using any previous hormonal treatment for endometriosis as well as oral and other contraceptive treatment to enable assessment of the effect of HSD17β1 inhibition by OG-6219 on ERP, and menstrual regularity of the endometrium (refer to the Table 2 and Appendix 7).

Embryo-fetal survival and development during the organogenesis phase of pregnancy was studied in pregnant rats and cynomolgus monkeys and no effect of OG-6219 treatment was found at the respective highest doses tested. However, as the effect of OG-6219 on fertility and early embryonic development and pre-and post-natal development has not been studied at this time, the risk of reproductive toxicity cannot be considered fully characterized. Therefore, necessary precautions to prevent pregnancy will be taken in this study. Participants will be informed about the risks to become pregnant and should not plan to become pregnant over the course of the study; only participants who are abstinent, or who are willing to reliably use an acceptable effective method for contraception as described in detail in the protocol (refer to the Appendix 5) and informed consent, or in whom safe contraception is achieved by a permanent method, will be eligible. A negative serum β-human chorionic gonadotropin (β-hCG) test prior to randomization and start of the treatment will be required, and monthly urinary pregnancy tests will be performed during the study implementation. Any pregnancy

will trigger withdrawal from study treatment, participant to expedited reporting and outcome of the pregnancy will be followed.

OG-6219 and its primary metabolite FOR-1011 are both metabolized primarily by Cytochrome (CYP) CYP3A4. No reversible or time-dependent inhibition of any CYP enzymes was observed for either OG-6219 or FOR-1011 at relevant concentrations in vitro, but both compounds induce CYP3A4 in a concentration-dependent manner. Clinical drug interaction studies were not performed yet. Therefore, concomitant administration of moderate and strong CYP3A4 inhibitors and inducers and sensitive substrates of CYP3A4 will be prohibited. OG-6219 and FOR-1011 were found to inhibit P-glycoprotein (P-gp) and/or Breast Cancer Resistance Protein (BCRP) transporters in vitro, thus concomitant administration of OG-6219 with sensitive P-gp and BCRP substrates should be avoided (see Appendix 7). Concomitant medications that are sensitive substrates of P-gp or BCRP should be administered at least 4 hours apart from administration of OG-6219.

In both toxicology species (rat and cynomolgus monkeys), statistically significant increases in liver weights were observed in OG-6219 treated groups which may be attributed to CYP3A4 induction. Full recovery was observed. No effect on biomarkers of hepatic function, including liver enzymes, albumin, and bilirubin was observed and there were no microscopic changes in the liver. In Phase 1 in a total of 71 participants treated with OG-6219 for up to 14 days at doses up to 150 mg BID, no clinically relevant changes in indicators of liver function were observed. However, no clinical data on effects on liver function with longer exposure are available. To manage the risk of potential hepatotoxicity, participants with pre-existing clinically, or serologically identifiable liver disease will be excluded, and liver function will be monitored via laboratory assessments throughout the study in monthly intervals.

OG-6219 and FOR-1011 displayed inhibition of the hERG channel potassium current with half maximal inhibitory concentration (IC50) values of CCI [redacted], respectively, indicating a potential risk of QTc prolongation. Both compounds are however highly bound to plasma proteins, resulting in low free concentrations in vivo and no cardiovascular toxicity or effects on ECG were observed in the in vivo cardiovascular safety study in cynomolgus monkeys. No clinically significant ECG changes were observed in Phase 1 with intense monitoring. To manage the risk of a proarrhythmic activity, in the Phase 2a/b study, ECG recordings at Screening aim to identify and exclude participants with clinically significant cardiac abnormalities. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E14 Clinical Evaluation of QT/QTc Interval prolongation and proarrhythmic potential and non-antiarrhythmic drug recommends that ECG recordings be performed at time points of expected C_{max}. Therefore, ECG recordings and vital sign measurements will be performed at CCI [redacted]

CCI [redacted] at each subsequent visit until the End of Study (EOS).

CCI [redacted]

[redacted] The ultraviolet (UV) absorbance of OG-6219 has a local maximum close to the low end of the natural sunlight wavelength range resulting in molar extinction coefficients values higher than the limit value of 1000 at wavelengths in the UVB spectrum below 305 nm. The penetration of UVB light into human skin is mainly limited to the epidermis and the clinical relevance of photochemical activation by UVB is therefore considered less important than activation by UVA for systemic drugs. The molecular structure of OG-6219 has been evaluated in silico with no alerts for photo-induced genotoxicity, chromosome damage, or photomutagenicity. In addition, no relevant distribution of OG-6219 to the skin or eyes was observed in a pre-clinical study in albino animals. Although, the binding affinity of OG-6219 to melanin has not been evaluated, the risk for phototoxicity of OG-6219 is considered minimal based on the totality of the available data and no specific precautions are therefore warranted.

As it has been requested by the United States Food and Drug Administration (FDA) and based on reported association between chronic pain conditions (eg, ERP) and depression, suicidality will be monitored throughout the study employing a validated questionnaire C-SSRS at each visit. Based on determination of positive C-SSRS results for suicidality, the participants will be discontinued from the study medication and referred to a specialist at the Investigator's discretion for further evaluation. In addition, the positive results from C-SSRS evaluation will

have to be treated as an SAE and reported to the Sponsor in a timely manner. CCI [redacted] by the Data Monitoring Committee [DMC] committee. Adverse Events and AESIs will be monitored throughout the study (at ongoing and pre-defined windows, as part of each DMC meeting to assess safety according to the DMC Charter).

The OG-6219-P001 DMC is an external group of independent experts assessing the safety data of the study on a regular basis. The DMC will be reviewing available clinical data at scheduled timepoints, as described in the DMC Charter, as well as on an ad hoc basis (urgent), as needed. DMC and Organon will conduct periodic reviews of the safety parameters during the course of the study and DMC ad hoc meetings may be convened at the discretion of DMC or if requested by Organon, if its regular scheduled reviews of aggregate safety data, identifies a potential signal of a serious risk. Organon may also ask the DMC to review any individual AEs thought to be of major significance; such events would generally include deaths or other serious outcomes, CCI [redacted]

[redacted]

Please refer to the current version of Investigator's Brochure (IB) for OG-6219 for additional precautions and potential AEs.

2.3.2 Benefit Assessment

There is a high medical need for new treatment options that are both effective and can be used long-term without modification of the HPG axis with the induction of a hypoestrogenic, hyperprogestagenic, or hyperandrogenic status with subsequent multiple systemic liabilities. OG-6219 is a novel HSD17β1 enzyme inhibitor being developed for the treatment of moderate to severe ERP. The pharmacological action of OG-6219 is based on its potent and selective binding to HSD17β1 and ability to locally inhibit E2 production. However, it has not been demonstrated that this results in pain reduction.

Estrogen-driven inflammation is thought to be the central process that shapes the pathology of endometriosis. Local inhibition of estrogen synthesis should, simultaneously, reduce proliferation of endometriotic lesions and avoid shedding of the ectopic endometrium theoretically modifying the vicious cycle of growing, bleeding, inflammation, and pain generation.

Participants with a surgical diagnosis (laparotomy or laparoscopy) of endometriosis and moderate to severe ERP will be randomized to be treated orally BID with either CCI , or matching Placebo for CCI menstrual cycles).

CCI At the tested doses of CCI BID, albeit with a wide variation, the combined endometrial concentrations of OG-6219 and its primary active metabolite FOR-1011 at Day 10 of dosing, approached or exceeded CCI equivalent to approximately CCI , over the dosing interval of 12 hours. At a concentration of CCI , OG-6219 inhibited E1 to E2 conversion by an average of CCI in ovarian endometriosis tissue homogenates ex vivo. Assuming that similar tissue concentrations in endometrial lesions will be reached as measured in eutopic endometrium (endometrium normally located inside the uterus) in healthy pre-menopausal participants, the doses and dose regimen chosen for this Phase 2a/b PoC, dose-range study are expected to result in local inhibition of HSD17β1 and therefore reduction in local E2 synthesis in endometriotic lesions as seen ex vivo. This Phase 2a/b study aims to establish the relevance of this inhibition for reducing ERP. Participants will have a CC chance to be randomized to OG-6219.

2.3.3 Overall Benefit Risk Conclusion

Current medical treatments for ERP provide similar, suboptimal pain control and have safety and tolerability issues that limit their use, often leading patients to have repeated surgical interventions. Thus, there is a need for development of new ERP medical therapies. A local inhibition of estrogen production at the ectopic implants level, for treatment of ERP, such as OG-6219, an oral, potent, selective inhibitor of HSD17β1 which can avoid the systemic adverse impact of hormonal treatments.

OG-6219 is a novel HSD17β1 enzyme inhibitor being developed for the treatment of moderate to severe ERP. The pharmacological action of OG-6219 is based on its potent and selective binding to HSD17β1 and ability to locally inhibit E2 production. The Phase 2a/b PoC and dose-range study aims to assess the efficacy, safety, and tolerability of 3 dose levels of OG-6219 on ERP (CCI BID). Phase 1 data demonstrated pharmacologically relevant endometrial exposure in healthy pre-menopausal participants at 2 higher doses tested (CCI BID and CCI BID). The lower doses of CCI BID are planned based on Phase 1 PK modeling data. CCI

OG-6219 was found to be safe and well-tolerated in Phase 1 with exposure of a total of 71 participants, of which 37 participants were pre-menopausal; 10 pre-menopausal participants were treated with the highest dose of 150 mg BID for 14 days during the first half of the menstrual cycle. No serious or severe AEs were reported. CCI

CCI [redacted] In the Phase 2a/b study, participants will be randomized to be treated with 3 dose levels of OG-6219 (CCI [redacted] BID), or Placebo for approximately CCI [redacted] (up to CC cycles, not longer than CCI [redacted] of study treatment exposure).

Most relevant pre-clinical findings that may be indicative of safety risks include hERG channel inhibition in vitro CCI [redacted] concentrations of both parent (OG-6219) and primary metabolite (FOR-1011), however, both OG-6219 and FOR-1011 are highly bound to plasma proteins resulting in low free concentrations in vivo and no pre-clinical nor Phase 1 evidence of QC prolongation has been found. CCI [redacted] An increase in liver weight in both rats and cynomolgus monkeys likely attributable to CYP3A4 induction; however, no pre-clinical or Phase 1 data suggest any potential liver toxicity. In addition, no data on fertility and early embryonic development are available. CCI [redacted] Therefore, in this current Phase 2a/b study, comprehensive panels assessing hematology, clinical chemistry, urinalysis parameters (CCI [redacted]), will be closely monitored. Refer to Section 8.4.6 for details of AESIs.

OG-6219 and its primary metabolite FOR-1011 are both metabolized mainly by CYP3A4 and were found to induce CYP3A4 in vitro. No clinical drug interaction studies were conducted to date. However, concomitant administration of OG-6219 with sensitive P-gp and BCRP substrates should be avoided (see Appendix 7).

To manage these risks, necessary precautions to prevent pregnancy will be taken in this study, including pregnancy tests prior to and during the study, and acceptable effective methods of contraception are required for participation. The effect of OG-6219 on systemic hormones, as well as general safety, including ECG and bone effects, will be closely monitored, including blood draws at different points during the first treatment cycle visit and each site visit at the start of next C treatment cycles, as well as during safety follow-up. Cycle length will be monitored by self-reported bleeding pattern in an eDiary. The ECG measurements will be performed at relevant exposure time points, including T_{max} on Day 1 at the Randomization Visit and after achieving steady state (visit at CC of the first menstrual cycle after randomization). CCI [redacted]. Suicidality will be monitored throughout the study employing a validated questionnaire C-SSRS. Based on

determination of positive C-SSRS results for suicidality, the participants will be discontinued from the study medication and referred to a specialist at the Investigator's discretion for further evaluation. In addition, the positive results from C-SSRS evaluation will have to be treated as an SAE and reported to the Sponsor in a timely manner. Concomitant medications that are sensitive substrates, as well as moderate or strong inhibitors or inducers of CYP3A4 are prohibited. Concomitant medications that are sensitive substrates of P-gp or BCRP should be administered at least 4 hours apart from administration of OG-6219.

Although OG-6219 absorbs light at a limited wavelength range the risk for phototoxicity of OG-6219 is considered minimal based on the totality of the available data and no specific precautions are therefore warranted.

Participants' safety and related AESIs will be continuously monitored by the Sponsor and by the DMC committee. Adverse Events and AESIs will be monitored throughout the study (at ongoing and pre-defined windows, as part of assessments according to the DMC Charter).

With these risk measures in place, the Sponsor believes that for this stage of development the potential benefits outweigh the risks for the Phase 2a/b study in participants with moderate to severe ERP.

3.0 OBJECTIVES AND ENDPOINTS

This is a double-blind, Placebo-controlled, parallel group, randomized study aimed to assess the efficacy, safety, and tolerability of OG-6219 in adult participants with moderate to severe ERP (OPP, DYS, and NMPP). The study objectives and endpoints are outlined in Table 1.

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary Endpoints The following primary efficacy endpoint will be assessed comparing Group A (CCI BID), B (CCI BID), C (CCI BID) with Group D (Placebo)	
• To evaluate the efficacy of 3 dose levels of OG-6219 (Group A, B, C) versus Placebo (Group D) in reducing OPP during TRC3, as measured by a NRS in the eDiary	• Change from BC to TRC3 in the mean OPP score[a]
The following primary safety endpoints will be assessed for Group A (CCI BID), B (CCI BID), C (CCI BID) and Group D (Placebo)	
• To evaluate the safety and tolerability of OG-6219	• Proportion of participants who experienced any AEs/SAEs • Abnormalities in clinical laboratory assessments, vital signs, and physical examination • Proportion of participants who prematurely discontinued study treatment due to AEs/SAEs
Secondary Efficacy Endpoints	
The following secondary endpoints will be assessed comparing Group A (CCI BID), B (CCI BID), C (CCI BID) with Group D (Placebo)	
1. To evaluate the efficacy of 3 dose levels of OG-6219 (Groups A, B, C) versus Placebo (Group D) in reducing DYS during TRC3, as measured by a NRS in the eDiary	• Change from BC to TRC3 the mean DYS score
2. To evaluate the efficacy of 3 dose levels of OG-6219 (Groups A, B, C) versus Placebo (Group D) in reducing NMPP during TRC3, as measured by a NRS in the eDiary	• Change from BC to TRC3 the mean NMPP score
3. To evaluate the efficacy of 3 dose levels of OG-6219 (Group A, B, C) versus Placebo (Group D) reducing dyspareunia during TRC3, as measured by a NRS in the eDiary	• Change from BC to TRC3 in the mean dyspareunia score
4. To evaluate the daily use of Sponsor provided rescue medication taken for ERP at TRC1, TRC2, and TRC3	• Change from BC to TRC1, TRC2, and TRC3 in the mean number of tablets of rescue medication for ERP • Change from BC to TRC1, TRC2, and TRC3 in the proportion of days participant has used rescue medication for ERP

Objectives	Endpoints
5. To evaluate the change in the PGI-S Score at different time points	• Change in PGI-S Score from C to Phone Contact CCI
6. To evaluate the change in the PGI-C Score in different time points	• Percentage of participants with any improvement on the PGI-C at TRC1, TRC2, and TRC3
7. To evaluate the change in the EHP-30 domains (CCI) from BC to TRC3	• Change from BC to TRC3 in the EHP-30 Domain Scores
Secondary Safety Endpoints	
8. To assess the incidence of clinically significant[d] changes from V1 to C in bone biomarkers: ○ CCI ○	• Mean change from V1 to C in bone biomarker levels
9. To assess the incidence of any clinically significant[d] changes in laboratory parameters from V1 to CCI	• Proportion of participants with clinical parameters of significance from V1 to CC I
10. To assess vaginal bleeding pattern over the 3 menstrual cycles (TRC1, TRC2, and TRC3) as captured in the eDiary	• Mean change from BC to TRC1, TRC2, TRC3 in the percentage of days with vaginal bleeding
11. To assess any potential change in the ECG parameters at CCI	• ECG parameter changes at CCI
Secondary PD / PK Endpoints	
12. To assess the change from CCI in serum hormone[b] concentrations	• Mean change from CCI in serum hormone levels
13. To assess any difference in serum hormone[b] concentrations at C between active treatment versus placebo	• Serum hormone levels comparing Group A (CCI BID), B (CCI BID), C (CC I BID) with Group D (Placebo)
14. To assess any difference in serum hormone[b] concentrations at C between active treatment versus placebo	• Serum hormone levels at V7 comparing Group A (CCI BID), B (CCI BID), C (CCI BID) with Group D (Placebo)
15. To assess the PK of orally administered OG-6219 and the active metabolite FOR-1011 using sparse and intensive[c] PK sampling.	• Plasma concentrations of OG-6219 and FOR-1011 at scheduled assessments using sparse PK sampling during the treatment period. • C_{max}, T_{max}, and AUC_{tau} for both OG-6219 and FOR-1011 on C and C for the population with intensive PK sampling
CCI	

CCI	[redacted]

Note: Refer below and to Figure 1

- Screening Cycle is between CCI .
- Baseline Cycle is defined as CCI which starts at C (first day of the menses) and ends at one-day before next menses.
- Treatment Cycle 1 is the period between the first day of menses associated with treatment start (C) to the day prior to the first day of next menses, regardless of number of days.
- Treatment Cycle 2 is the period between the first day of second menses after end of BC to the day prior to first day of next menses, regardless of number of days.
- Treatment Cycle 3 or EOT is the period between the first day of third menses after end of BC to either end after CCI on study treatment, whichever occurs first.
- Safety Follow-up Cycle is the period time between the first day after stopping study treatment during TRC3 and ends after 30 consecutive days.

a. OPP score is defined as the combination of the DYS and NMPP scores in a cycle
b. CCI [redacted]
c. Intensive PK sampling is optional and applicable for subset of PK analysis set, where a separate consent would be provided.
d. Clinical significance is defined as any variation in physical findings or laboratory assessments that has medical relevance and may result in an alteration in medical care refer to Section 8.3.1 and Section 8.3.7.

Abbreviations:

AE=Adverse event

CCI [redacted]

ECG=Electrocardiogram;

BC=Baseline Cycle;

C-SSRS=Columbia-Suicide Severity Rating Scale;

CCI [redacted]

DYS=Dysmenorrhea;

CCI [redacted]

eDiary=Electronic diary;

EHP-30=Endometriosis Health Profile-30;
CCI
CCI
NMPP=Non-menstrual pelvic pain;
CCI
PGI-S=Patient Global Impression of Severity;
SC=Screening Cycle;
CCI
TRC1=Treatment Cycle 1;
TRC3=Treatment Cycle 3;
V=Visit;
CCI
EOT=End of Treatment;
ERP=Endometriosis-related pain;
NRS=Numeric rating scale;
OPP=Overall Pelvic Pain (endometriosis-related);
PGI-C=Patient Global Impression of Change;
PK=Pharmacokinetic;
CCI
TRC2=Treatment Cycle 2;
CCI

Estimands

Details regarding estimands will be including in the Statistical Analysis Plan (SAP).

4.0 STUDY DESIGN

4.1 Overall Design

This global multicenter, Phase 2a/b, randomized, double-blind, Placebo-controlled, 4-arm PoC, dose-range study is to assess the efficacy, safety, and tolerability of 3 dose levels of OG-6219 (CCI BID), in pre-menopausal women 18 to 49 years of age (inclusive), who have been surgically diagnosed with endometriosis within the last 4 months to 10 years prior to V1 and with moderate to severe ERP. Participants should be off hormonal treatments following the timeframe indicated in the Table 2 (Exclusion Criterion # 31).

The study duration of approximately 28 weeks includes: an initial period of 2 to 4 weeks approximately, between V1 and CCI to collect safety laboratory assessments. Each cycle refers to 1 menstrual cycle of around 21 to 32-day duration. A Screening Cycle (SC), between CC and CCI; A BC or Single-blind CCI, between CC and CCI. A Randomization Visit CCI, to treatment allocation with a ratio of CCI to 3 active arms and 1 Placebo arm. This is a double-blind treatment cycle across 3 menstrual cycles, Treatment Cycle 1 (TRC1), Treatment Cycle 2 (TRC2), and Treatment Cycle 3 (TRC3) or End of treatment (EOT); and is followed by a Safety Follow-up Cycle (SFC). Overall, the study includes C on-site visits, C phone contacts, as detailed below:

- Screening Period:
  - One SC: Starts at CC (first day of the menses) and ends one-day before next menses.
  - One BC during the single-blind, CCI period: Starts at CC (first day of the menses) and ends at one-day before next menses.
- Randomization: CC, this is on first day of the next menses after the end of BC.
- Treatment Period: Three treatment cycles (TRC1, TRC2, and TRC3) after CC:
  - TRC1 is the period between the first day of menses associated with treatment start (CC) to the day prior to the first day of next menses, regardless of number of days. CCI
  - TRC2 is the period between the first day of second menses after end of BC to the day prior to first day of next menses, regardless of number of days. Phone Contact 1 is done during the menses.
  - TRC3 or EOT is the period between the first day of third menses after end of BC to either end after C completed cycles or CCI on study treatment, whichever occurs first.
- Safety Follow-up:
  - SFC, is the period of time between the first day after stopping study treatment during TRC3 and ends after 30 consecutive days (regardless of whether it aligns with first day menses or not). Phone contact C is done CCI after last intake of study treatment. Visit C at the first day of next menses is considered EOS.

At CC, participants will receive the eDiary which will be used CCI until the EOS (CC) to collect the CCI (worst) pelvic pain scores (DYS, NMPP, dyspareunia). The pain score entered CCI by each participant in the eDiary must capture the CCI

corresponding to that day and should be entered at about the same time (before going to bed). The eDiary will also collect CCI [redacted] as well as mental health assessment via C-SSRS will be collected according to the SoA (Section 1.3).

An external DMC will conduct periodic reviews of safety parameters during the course of the study in accordance with the DMC charter.

Please refer to Schedule of Activities (SoA), Section 1.3 for details about assessments to be performed during each visit.

4.2 Scientific Rationale for Study Design

Organon is developing OG-6219 as a novel, HSD17β1 enzyme inhibitor for the treatment of moderate to severe ERP. The pharmacological action of OG-6219 is based on its potent and selective binding to HSD17β1. The OG-6219 is not expected to interfere with the biological effects of systemic circulating estrogen because the putative mechanism of action is based on its ability to inhibit local conversion of E1 to E2 in endometriotic lesions.

As part of a single/multiple ascending dose Phase 1 study, 37 pre-menopausal women treated with doses up to CCI [redacted] BID of OG-6219 for 14 days showed the absence of effects on the HPG axis, along with demonstrating safety and tolerability up to the highest tested dose. FOR-1011 was identified as the primary and active metabolite of OG-6219, with a similar potency to inhibit HSD17β1 as the parent compound; OG-6219 and FOR-1011 have an additive effect on inhibition of HSD17β1. In Phase 1, FOR-1011 was found to accumulate and appeared to reach steady state within 14 days, the end of the treatment period in the Phase 1 study.

In this Phase 2a/b, multicenter, randomized, Placebo-controlled, double-blind, PoC, dose-range study in pre-menopausal women with moderate to severe ERP, the effect of OG-6219 on endometriosis-related OPP, DYS, NMPP, and QoL as measured by the EHP-30, a validated instrument in endometriosis patients, will be collected in the eDiary to assess the clinical efficacy of OG-6219. In addition, safety, and tolerability will be monitored. A 1 cycle safety follow-up period is implemented to exclude late effects on safety and tolerability and evaluate any possible residual therapeutic benefit.

A double-blind, randomized, Placebo-controlled design of the study was chosen to account for the well-known Placebo effect on ERP. A CCI and to reinforce compliance with the CCI entries in the eDiary. At the Randomization Visit (CC) there will be an assessment of the eligibility based on pain score, compliance with the eDiary, compliance with the use of study treatment and rescue medication. This will determine whether a participant can be randomized. The Phase 2a/2b design assessing CCI of treatment was chosen to evaluate the efficacy, safety, and tolerability of 3 dose levels of OG-6219, in pre-menopausal women with ERP. In previous Phase 2 studies conducted in ERP, C menstrual cycles have been the standard for evaluating pain improvement.[50-52] Additionally, HSD17β1 inhibitor treatment for 8 to 12 weeks in marmoset endometriosis model demonstrated an effect in number of lesions with regression and reduction in size.[28]

This is a PoC, dose-range study aiming to assess the effects of multiple doses of OG-6219 compared to Placebo in participants with moderate to severe ERP and provide evidence that the hypothesized mechanism of pain generation is modified by the OG-6219. The protocol has a CCI to provide a baseline pain score and further assessments of study intervention (OG-6219 or Placebo). Participants will receive OG-6219 or Placebo in a CC ratio during the study. The inclusion and extent of exposure of the Placebo group is in accordance with current health authority guidelines.[53-55] The inclusion of a Placebo control group is considered essential to the design of this study because a Placebo arm is necessary to allow an accurate assessment of the efficacy, safety, and tolerability of OG-6219. Comparison of OG-6219 to Placebo will optimize the interpretability of efficacy, safety, and tolerability data.

Phase 1 data in healthy pre-menopausal participants treated with OG-6219 for 14 days demonstrated CCI . At the tested doses of CCI BID, albeit with a wide variation, the combined endometrial concentrations of OG-6219 and its primary active metabolite FOR-1011 at Day 10 of dosing approached or exceeded CCI equivalent to approximately CCI over the dosing interval of 12 hours. CCI

4.3 Justification for Dose

It is planned to study 3-dose levels of OG-6219 (CCI BID) to obtain data on dose dependency of the effect of OG-6219 on ERP. The highest dose will be CCI BID CCI . At that dose, CCI , with combined tissue concentrations of OG-6219 and FOR-1011 over the entire dosing interval

above IC 90 for the inhibition of HSD17β1 in endometriotic lesions ex vivo. The lower doses of CCI were chosen based on modeling of Phase 1 PK data to achieve lower local concentrations, still however remaining around and above the ex vivo IC90 of the combined exposure to OG-6219 and FOR-1011 over the dosing interval.

The plasma-concentration curve of OG-6219 suggests BID dosing is required with the current immediate release tablet formulation to achieve adequate inhibition of HSD17β1 over 24 hours.

The Phase 2a/b study will be conducted using a tablet formulation. The relative bioavailability of OG-6219 in the tablet formulation was similar to that of the liquid formulation used in the single ascending dose/multiple ascending dose study in terms of AUC, while the C_{max} was lower (geometric mean ratio of 0.70). Since there was no meaningful difference on the bioavailability of OG-6219 when given as the tablet formulation between fed and fast state, there will be no restriction with regards to food intake relative to dosing of OG-6219 in this study, refer to IB.

4.4 End of Study Definition

The EoS is defined as the date of the last visit of the last participant in the study Visit CCI.

A participant is considered to have completed the study if she has completed all phases of the study, including the last scheduled procedure indicated at the EOS Visit shown in the SoA; Section 1.3.

5.0 STUDY POPULATION

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

5.1 Inclusion Criteria

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

1. Pre-menopausal females* of age 18 to 49 years old (inclusive) at the time of signing Informed Consent (V1).
2. Surgically (laparoscopy or laparotomy) diagnosed with endometriosis within the last 4 months to 10 years prior to Screening Visit (V1), as documented by medical records.
3. Has moderate to severe endometriosis-related pelvic pain in recent menstrual cycle(s) using a cutoff score of ≥4 in a numeric rating scale (NRS) and likely meets eligibility criterion # 10 at Randomization Visit CCI .
4. Has had spontaneous (ie, without hormonal therapy), regular, menstrual cycle with a cycle length between 21 to 32 days (inclusive) for the past 1 month before V1. **Note**: Peri-menopausal women have irregular menstrual cycles, and don't meet this inclusion criterion, and should not be included.
5. Is not expected to undergo a planned gynecological surgery or other surgical procedures for treatment of endometriosis during study participation.
6. Has a normal breast examination at V1. In participants of ≥40 years mammography or contrast-enhanced breast MRI performed within the last 12 months prior to Screening (V1) without clinically significant abnormal findings.
   Note: Participant with Breast Imaging-Reporting and Data System Classification 1 to 3 is eligible for randomization.
7. Agrees not to participate in another interventional study while participating in the present study.
8. Is able and willing (in the opinion of the Investigator) to adhere to all required study procedures, including:
   a) Study visits schedule,
   b) Agree to switch from their usual analgesic to ONLY the rescue medication provided by the study and agree to discontinue their hormone treatment for ERP as outlined in Table 2.
   c) Agree to timely and duly complete eDiary entries,
   d) To cooperate and comply with the protocol requirements, including, TVUS, ECG, PK, and pharmacodynamic (PD) assessment among others.
   Note: If participant cannot tolerate or withstand a TVUS, a trans-abdominal ultrasound may be considered as an option, as per the Investigator discretion.

e) Agree to use 2 forms of non-hormonal contraception throughout the study (from V1 thorough CC).
Note: Hormonal contraception is not permitted in the study. Women of childbearing potential must use adequate non-hormonal contraceptive methods to prevent pregnancy. Contraception must be used throughout the study starting at V1 through to CC. The sporadic use of emergency contraception is permitted during the study. Refer to the Appendix 5 to review the non-hormonal contraceptives method for this study.
f) Not planning to relocate during the study (such that the participant would not be able to continue participation at the study site).

9. Must be willing and able to provide signed informed consent before any study-related activities.

At Visit CC: Inclusion Eligibility Criteria:

10. Has moderate to severe ERP, determined by the NRS (0 to 10 anchored, with 0 [no pain] and 10 [extremely severe pain]), at CC (before Randomization), based on the eDiary entries from the participant's last menstrual cycle (BC), as follows:
    a) An OPP (DYS and NMPP) CCI , OR
    b) For DYS at least 2 days with CCI CCI , OR
    c) For DYS at least 2 days with CCI (not necessarily consecutive).
11. Has demonstrated compliance with CCI of eDiary entries (ie, pelvic pain score, vaginal bleeding, rescue medication intake) during both the SC and the BC.
    Note: eDiary compliance will be automatically calculated by the eDiary vendor portal and a report will be provided. The Investigational study site should review the report before the participant's schedule visit to assess eligibility at Randomization Visit CCI .
12. Is CCI compliant with the Placebo tablets over the BC (CCI), as determined by tablet accountability at the site.
13. Has taken only the study provided rescue medication, at a dose not exceeding the maximum dose determined by the Investigator, for control of ERP during the BC as evidenced in the eDiary.
    CCI
14. Have a negative pregnancy test as outlined in the SoA (Section 1.3).

* Please contact the Medical Monitor surrounding non-binary participants eligibility in the clinical study.

5.2 Exclusion Criteria

Participant is excluded from the study if any of the following criteria apply:

Gynecological Medical Conditions

1. Has a surgical history of hysterectomy and/or bilateral oophorectomy.
   Note: Participants who have undergone surgical sterilization (eg, bilateral salpingectomy, tubal ligation, or unilateral oophorectomy) are permitted in the study.
2. Has chronic pelvic and/or non-pelvic pain NOT CAUSED by endometriosis that requires chronic analgesic or other chronic therapy (including, but not limited to, pain caused by interstitial cystitis, bladder pain syndrome, irritable bowel syndrome, hysteroscopic sterilization, adenomyosis [as confirmed by previous MRI], vaginismus, chronic pelvic infection, fibromyalgia, chronic headaches, chronic back pain). Participants using or who will be using frequent opioid analgesics, cannabis, or non-opioids analgesics for chronic pain or recurring pain other than that due to ERP should also be excluded.
3. Has a clinically significant gynecologic condition identified in the screening (including, but not limited to, CCI [redacted].
4. Has a history of ERP that was not responsive at all (refractory) to treatment with CHCs, GnRH agonists and antagonists, progestins, or aromatase inhibitors alone or in combination. The participant that required >2 weeks of continuous use of narcotics for treatment of ERP within 6 months of V1 should also be excluded.
   Note: Participants who achieved a partial response or were treatment failures due to side effects should not be excluded.
5. Had undiagnosed (unexplained), abnormal, vaginal bleeding not associated with the baseline condition (endometriosis) within the past 6 months before screening.
   Note: Participants may be rescreened after completing treatment for simple ovarian cysts.
6. Has an active sexually transmitted infection (STI) (eg, gonorrhea, chlamydia, or trichomonas) is exclusionary.
   Note: Participants may be rescreened after completing treatment for infection.
7. Has no documented normal Papanicolaou (PAP) test within the timeline of current standard of care guidelines or has a significantly abnormal PAP test at Screening (V1) (ie, low-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion, atypical glandular cells [any type], squamous cell carcinoma, or adenocarcinoma [in situ or invasive]). The presence of high-risk human papillomavirus (HPV), regardless of PAP result, is exclusionary (e.g. atypical squamous cells).
8. Intends to become pregnant during study participation or has a known or suspected pregnancy or has a positive β–hCG or urine pregnancy test at any time before randomization.

Note: If the urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

9. Has a history of malignancy (except basal cell or squamous cell skin cancer) before signing informed consent.
   Note: Any history of hormonal sensitive malignancy (e.g., breast or ovarian cancers) excludes the participant

Other Medical Conditions:

CCI

[redacted]

12. Has an allergy/sensitivity/intolerance to rescue medication provided by Sponsor or any contraindication to its use and in the setting of coronary artery bypass grafting surgery, or has experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs,
13. Has a history or current evidence of any unstable medical condition (including cardiovascular, bone, musculoskeletal, thyroid, diabetes), or other circumstance that in the opinion of the Investigator might confound the results of the study, affect participant's safety or well-being, or interfere with the participant's participation for the full duration of the study.
14. Has a known human immunodeficiency virus infection, and/or an acute or active, recurrent/relapsing, or chronic infection (eg, hepatitis A, B, or C virus).
15. Has a gastrointestinal, liver, kidney, or other disorder that would significantly interfere with the absorption, distribution, metabolism, or excretion of drugs in the opinion of the Investigator.
16. Has a clinically significant abnormal ECG or QT interval prolongation at Screening Visit (V1) or Randomization Visit CCI. Any participant with the following conditions must be excluded:
    a) A marked baseline prolongation of QT/QTc interval (eg, repeated demonstration of a QTc interval CCI milliseconds)
    b) A history of additional risk factors for Torsade de Pointes (eg, heart failure, hypokalemia, family history of Long QT Syndrome)
    c) Use of concomitant medications that prolong the QT/QTc interval (such as but not limited to: ibutilide, quinidine, imipramine, erythromycin, and droperidol).

17. Plans to schedule elective surgery during the study execution or had surgery in the past 4 months before screening that continues to require pain management.
18. Suspected active Coronavirus Disease 2019 (COVID-19) infection
    a) Have tested positive for severe acute respiratory syndrome–related coronavirus-2 (SARS-CoV-2) based on a validated test per local guidelines at Screening and Baseline
    b) Have to comply with quarantine requirements per local Public Health directive

    Note: Participants with clinical symptoms suggestive of COVID-19 can be rescreened after 14 days if symptoms resolve and the participant does not test positive for SARS-CoV-2.
19. Has been vaccinated with live or live-attenuated virus vaccine within 30 days prior to Screening.

Diagnostic Assessments

20. Has an uncontrolled hypertension as diagnosed by participant's treating physician.
21. Has any of the following abnormal laboratory values at Screening
    a) Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Gamma glutamyl transpeptidase >2 × upper limit of normal (ULN), Alkaline Phosphatase >1.5 × ULN, provided cholestatic or other liver disease is excluded
    b) Total bilirubin (TBL) >1.0 ULN (participants with Gilbert's syndrome can be enrolled if other liver function tests are within stated limits)
    c) Impaired renal function as indicated by estimated glomerular filtration rate <30 mL/min/1.73 m^2 (CKD-EPI 2009 calculation)
    d) Hemoglobin <10 gm/dL, white blood cell count <2500 mm^3, neutrophil count <1500 mm^3, platelet count <100 × $10^3/mm^3$.

Lifestyle

22. Based on the known metabolism of OG-6219 there are no effects of alcohol, caffeine, or tobacco associated with study treatment. However, during the study participants are asked to refrain from:
    a) Excessive tobacco use and smoking CCI [redacted] based on Investigator's discretion).

    CCI [redacted]
    b) Active use of illicit drugs and/or alcohol abuse/dependance, as determined by the Investigator.

    Note: Alcohol intake should be limited to 2 to 3 units per day, not to exceed 14 units per week.
23. Has a prior or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders 5 (DSM5). [66]

Prior/Concurrent Clinical Study Experience

24. Has undergone blood transfusion within 2 weeks of V1. In addition, has lost ≥1 unit of blood (approximately 300 mL) within 8 weeks before the first dose of OG-6219.
25. Use of treatments that might interfere with the conduct of the study or interpretation of the results (Appendix 7).
26. Used any medication listed in Appendix 7 that is either a sensitive substrate, moderate, or strong inhibitor or inducer of CYP3A4 within 30 days or 10 half-lives (whichever is longer) prior to the planned first day of dosing. Participants must not consume other substances known to be potent inhibitors or inducers of CYP P450s such as grapefruit or Seville oranges containing products in 2 weeks before the planned first dose of study treatment administration.
27. Current or a history of psychiatric disorder in the 3 years prior to Screening that would, in the opinion of the Investigator, affect the ability to participate in the study or would impair interpretation of data. Participants with current major depression, posttraumatic stress disorder, bipolar disorder, schizophrenia, or other psychotic disorders are excluded. Participant has a history of suicidal ideation or attempt within 3 years of Screening (V1).
    Note: Current depression that is being treated and stable is not exclusionary.
28. Has been a participant in an investigational drug or device study within 30 days prior to the Screening Visit.
29. A study site employee or relative of a study site employee.
30. Participant is pregnant, breast feeding, or planning a pregnancy within the next 7 months.
31. Participants has received any treatment listed in Table 2 more recently than the "Last Allowable Use", as indicated in the table, or must continue to receive any treatment listed in Table 2 during the study.

Table 2 Prohibited Medication, Contraceptive Devices and Other Substances

The following medications, contraceptive devices and other substances are prohibited at any time during the participant's participation in this study (excluded from the time point specified below throughout the study):

Prohibited Medications: Hormones and Contraceptive Devices	Last Allowable Use
• Progestogens, GnRH agonists, menotropins, and human chorionic gonadotropin (hCG)	• 3 months before Visit 1
• Injectable GnRH with 3-month duration (eg, leuprolide)	• 10 months before Visit 1
• Oral, patch, and implanted contraceptives; vaginal ring, and medicated intrauterine device (IUD)	• 1 month before Visit 1[a]
• GnRH antagonists or aromatase inhibitors	• 1 month before Visit 1
• Injectable hormonal contraception with 1-month duration	• 3 months before Visit 1
• Injectable hormonal contraception with 2-month duration	• 6 months before Visit 1
• Injectable hormonal contraception with 3-month duration	• 9 months before Visit 1
• IUD (non-hormonal)	• Before Visit 1[b]
• Hormonal Replacement Therapy (HRT)	• Before Visit 1
Prohibited Medications: Analgesics	**Last Allowable Use**
• NSAIDs (eg, aspirin, ketorolac) ○ Protocol-specified rescue medication is permitted. • COX-2 inhibitors • Other non-specified analgesics (eg, acetaminophen or paracetamol)	• At CCI
• Opioid analgesics (eg, tramadol and tapentadol)	• 5 days before CCI
Prohibited Medications: Other	
• Herbal remedies containing Hypericum perforatum (eg, St. John's wort), and Kava • Cannabis-derived and cannabis-related compounds[d]	• At Visit 1
• Glucocorticoids (oral or intravenous)	• 2 months before Visit 1

a. Not including emergency contraceptive pills.
b. Participants with an IUD (non-hormonal) on the day of the Screening Visit are excluded.
CCI [redacted]

Abbreviations: COX-2=Cyclooxygenase-2; GnRH=Gonadotropin releasing hormone; NSAID=Nonsteroidal anti-inflammatory drugs.

5.3 Lifestyle Considerations

Participants must adhere to protocol-prescribed procedures to avoid pregnancy. This includes monthly pregnancy tests after start of treatment and reliable use of acceptable effective contraceptive methods.

Excessive tobacco uses and smoking has been restricted based on the Investigator's discretion. Abuse of alcohol is prohibited. Alcohol intake should be limited to 2 to 3 units per day, not to exceed 14 units per week. Active use of illicit drugs is prohibited.

Note: CCI [redacted] CCI [redacted] Refer to Table 2 for a list of prohibited medications.

Participants must refrain from consumption of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, and Seville orange juice or other products containing grapefruit or Seville oranges from 14 days prior to the first dose of study treatment and for the duration of the study treatment (ie, final dose).

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently allocated to treatment in the study CCI [redacted] A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographic data, reason for screen failure, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened except for; participants with diagnosis and treatment of chlamydia, gonorrhea, or trichomonas, if not at risk for reinfection; simple ovarian cyst adequately treated among other. Please refer to Section 5.2 for complete details. Participants may be rescreened on a case-by-case basis after discussion and approval by the Medical Monitor.

Rescreened participants retain the same participant number (Appendix 2). If the rescreening is outside the 42-day window since V1, all screening assessments must be repeated.

6.0 STUDY TREATMENT AND CONCOMITANT THERAPY

Study treatment is defined as any investigational intervention(s), marketed product(s), Placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Treatments Administered

Details of the treatments administered in this study (OG-6219 and Placebo to match OG-6219) are presented in Table 3.

Table 3 Study Treatment Administered

Study Treatment Label	OG-6219 CCI or Placebo	
Study Treatment Name	OG-6219	Placebo to match OG-6219
Type	Investigational	Placebo
Dose Formulation	White to off-white to light brown tablet, with or without mottling	White to off-white to light brown tablet, with or without mottling
Unit Dose Strength(s)	CCI	Not Applicable
Dosage	BID, arm dependent	Not Applicable
Route of Administration	Oral	Oral
Fill Counts	Bottle A: CCI Bottle B:	Bottle A: CCI Bottle B:
Dosing Instructions	Bottle A: CCI BID as directed. Bottle B: BID as directed.	Bottle A: CCI BID as directed. Bottle B: BID as directed.
Use	Experimental	Placebo
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Study treatment will be provided in bottles containing CCI labeled as "OG-6219 CCI or Placebo" to maintain the blind. The bottles will also be labeled as required per country requirements. Provided centrally by the Sponsor	Placebo will be provided in bottles containing either CCI labeled as "OG-6219 CCI or Placebo" to maintain the blind. The bottles will also be labeled as required per country requirements. Provided centrally by the Sponsor
Storage	CCI	

Abbreviations: BID=twice a day; V=visit.

Table 4 Treatment Arms

Treatment Arm Type	Placebo	OG-6219 CCI BID (Experimental)	OG-6219 CCI BID (Experimental)	OG-6219 CCI BID (Experimental)
Arm Treatment Description	Participants will receive OG-6219 CCI BID CCI [redacted]. Refer to Table 5 for dosing details.	Participants will receive OG-6219 CCI BID during double-blind Treatment Period CC [redacted]. Refer to Table 5 for dosing details.	Participants will receive OG-6219 CCI BID during double-blind Treatment Period CC [redacted]. Refer to Table 5 for dosing details.	Participants will receive OG-6219 CCI BID during double-blind Treatment Period CCI [redacted]. Refer to Table 5 for dosing details.

Abbreviations: BID=twice a day; V=visit.

Table 5 Blinded Study Treatment Overview

	Bottle A–OG-6219 CCI or Placebo CCI		Bottle B–OG-6219 CCI or Placebo CCI	
Treatment Arm	**OG-6219 CCI Active**	**OG-6219 CCI Placebo**	**OG-6219 CCI Active**	**OG-6219 CCI Placebo**
CCI **OG-6219 Placebo BID**	CCI BID		CCI BID	
OG-6219 CCI ID	CCI BID	CCI BID		
OG-6219 BID	CCI BID		CCI BID	C
OG-6219 BID	CCI BID	-	CCI BID	C
OG-6219 Placebo BID	CCI BID		CCI BID	

Abbreviations: BID=Twice a day.

Each participant will be dispensed 4 bottles (2 x Bottle A and 2 x Bottle B) for each treatment period to support up to CCI of dosing.

Bottle A will contain C OG-6219 CCI or Placebo tablets and Bottle B will contain C OG-6219 CCI or Placebo tablets.

Blinded doses are achieved by taking CCI from Bottle A (BID) and CCI from Bottle B (BID).

Table 6 Non-Investigational Medicinal Products / Rescue Medication

Medication Name:	Naproxen sodium
Type	Non-investigational medicinal product: Rescue medication
Dosage Formulation:	Tablet
Unit Dose Strength:	CCI
Route of Administration:	Oral
Dosing Instructions:	Take as directed.
Packaging and Labeling	Product will be provided in commercial packaging and will be labeled as required per country requirements.
Sourcing:	Provided centrally by the Sponsor. In special circumstances, may be provided locally with prior approval from the Sponsor.

6.2 Preparation, Handling, Storage, and Accountability

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received, and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment, and only authorized study site staff may supply or administer study treatment. All study treatment 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 study site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- For reporting of potential quality-related concerns with study treatments, refer to the Pharmacy Manual. Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual or other specified location.

The Investigator, a member of the study site staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study treatment using the Drug Accountability Form. These forms must be available for inspection at any time.

For further details, see current OG-6219 IB.

6.3 Measures to Minimize Bias: Randomization and Blinding

Randomization will be used to avoid bias in the assignment of participants to treatment groups. Eligible participants will be randomized in a CCI ratio at Randomization Visit CCI to receive one of 3 doses of OG-6219 or matching Placebo. CCI participants will be randomized to CCI the 4 study arms.

Participants will sign a separate consent for optional intensive PK prior to randomization. The study will be stratified based on consent to intensive PK (Yes/No) in order to ensure balanced treatment assignment within the intensive PK group.

The study site will contact the Interactive Response Technology (IRT) system to obtain the study treatment. Study treatment will be dispensed at the study visits summarized in the SoA (Section 1.3). Before the study is initiated, additional IRT directions and/or log in information will be provided to each study site.

Method of blinding:

The study is blinded for assignment of OG-6219 and Placebo. Tablets of OG-6219 and Placebo will appear identical.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted.

Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, he/she may, at his/her discretion, contact the Sponsor/designee to discuss the situation prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant.

If a participant's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

During the double-blind period, the following personnel will remain blinded to the treatment assignment: participants, Investigators, other study site personnel, clinical staff, Medical Monitor, study site monitors and other Sponsor representatives involved in the clinical aspects of the study conduct.

6.4 Study Treatment Compliance

The prescribed dosage and mode of administration may not be changed. Any deviations from the intended regimen must be recorded in the eCRF.

A record of the quantity of tablets administered by each participant must be maintained and reconciled with study treatment and compliance records.

All study treatment will be administered by the study site staff when the participant is at the site. Any non-compliance will be recorded in the eCRF. Non-compliance is defined as taking any dose (more or less) other than the protocol dose.

6.5 Dose Modification

Dose modifications are not applicable for this study.

6.6 Continued Access to Study Treatment after the End of the Study

The Sponsor will not provide additional care to the participants after they complete or discontinue the study.

6.7 Treatment of Overdose

No clinical data are currently available regarding OG-6219 overdose. For this study, any dose of study treatment that deliberately or accidentally administered by a study participant at a dose above that assigned to that individual participant according to a study protocol will be considered an overdose.

The Medical Monitor must be contacted in the event of any study treatment overdose.

In the event of an overdose, the Investigator or treating physician should:

- Contact the Medical Monitor immediately
- Closely monitor the participant for AEs including laboratory abnormalities
- All overdose events associated with SAE (including intentional suicidal/self-harming intent) must be reported within 24 hours by completing a SAE form (please refer to Section 8.4, Table 7)
- Overdose events associated with a non-serious AE must be reported within 5 calendar days of learning of event (please refer to section 8.4, Table 7)
- All other overdose cases not associated with AE/SAE must be captured in the appropriate section of eCRF
- If possible, obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis)

- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

The Medical Monitor, in consultation with the Investigator, will make decisions regarding participant status and potential dose interruptions, based on the clinical evaluation of the participant.

6.8 Concomitant Therapy

Prior treatments are defined as, i) all treatments (including prescription or over the counter [OTC] treatments and dietary supplements) taken by the study participant within 30 days prior to randomization and ii) medications no longer being taken when study treatment is given will be prior treatments.

Concomitant therapies are defined as, any medications (including OTC or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of signing the informed consent form (ICF) (within 14 days before the time of signing the ICF) or receives during the study must be recorded on the eCRF with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

Vaccination with live or live-attenuated virus vaccine within 30 days prior to Screening is prohibited. Administration of non-live vaccines (including SARS-CoV-2 vaccines) can be administered according to local vaccination standards whenever medically appropriate.

Any vaccination administration during the study should be recorded in the eCRF as a concomitant medication: all vaccine information should be collected, including brand name, manufacturer (and lot number if available) as well as administration dates.

6.8.1 Rescue Medication (Naproxen sodium)

Participants can use rescue medication for the management of ERP from CCI (EOS) only per instructions by the Investigator (Appendix 6). Use of the rescue pain medication will be recorded in the eDiary. Rescue medication is intended only for ERP and should not be used for any other pain. The use of the rescue medication as prophylactic for ERP is not allowed. The maximum dose of the rescue medication will be provided by the Investigator, following local guidelines, and should not be used differently.

The use of naproxen sodium for rescue medication will be reviewed at each study visit and during the telephone follow-ups. An eDiary report will identify if a participant has taken an overdose of rescue medication based on the local labeling, and the Investigator should follow-up with the participant and report the overdose as appropriate (Table 7).

6.8.2 Prohibited Medications and Other Products

The following concomitant medications, therapies, and products are prohibited during study participation (refer to Table 2, Appendix 6, and Appendix 7). Please note these additional clarifications for prohibited medications/products:

- Sensitive substrates, moderate, and strong inhibitors, or inducers of CYP3A4 (Appendix 7).
- Sensitive substrates of P-gp and BCRP
  Note: For the P-gp and BCRP substrates: they should be administered at least 4 hours apart from OG-6219 (Appendix 7).
- Endometriosis treatments for symptom relief except rescue medication allowed by protocol (Appendix 6).
  Note: Participants can NOT use local anesthetic (eg, lidocaine patches) NOR receive acupuncture while participating in the study
- The use of analgesic medication different than the rescue medication is prohibited (this is referred as prohibited pain medication, see Appendix 8).
  CCI [redacted]
- Surgical treatment of endometriosis and use of intrauterine devices are prohibited from start of the Screening Period until EOS.

6.9 Study Treatment Accountability

Records will be maintained by authorized staff of the delivery, receipt, dispensing, and return of study treatment to provide a complete accountability of the disposition of the study treatment. The quantity of dispensed study treatment will be entered into the IRT. The Participant number, amount of study treatment and date dispensed, date of return of used study treatment and amount returned will be recorded.

Note: The use of rescue medication will also be recorded in the IRT and eDiary.

6.10 Study Treatment Handling and Disposal

During the study all unused, returned or not dispensed study treatment will be retained at the study site and stored per instructions from the Sponsor. After the clinical monitor has performed final drug accountability review, the study site will either return or destroy excess study treatment according to Sponsor instructions in a separate Pharmacy Manual.

7.0 DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific study sites or of the study as a whole are detailed in Appendix 2.

7.1 Discontinuation of Study treatment

It may be necessary for a participant to permanently discontinue study treatment. If study treatment is permanently discontinued (eg, Safety recommendation based on DMC assessment), the participant will remain in the study to be evaluated for Safety. See SoA (Section 1.3) for data to be collected at the time of discontinuation of study treatment and follow-up and for any further evaluations that need to be completed.

If a participant who does not meet enrolment criteria is inadvertently enrolled, that participant must be discontinued from study treatment and the Sponsor, or Sponsor designee, must be contacted. An exception may be granted in rare circumstances for which there is a compelling safety reason to allow the participant to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor, or Sponsor designee, to allow the participant to continue in the study.

Participants who do not wish to conceive after the last dose of study treatment should begin a new contraceptive method as soon as possible. Post-study contraceptive counseling will be provided by study site personnel in accordance with the SoA (Section 1.3).

Participants who discontinue study treatment will not be replaced.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw consent from study participation at any time at her own request or may be discontinued at any time at the discretion of the Investigator or the Sponsor (described in detail below).

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued from the study treatment and the study at the same time.

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

If a participant withdraws from the study, she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

A participant's treatment and participation in the study may also be discontinued at any time at the discretion of the Investigator or the Sponsor. Justifiable reasons include, but are not limited, to:

- The participant withdraws consent to participate
- Investigator opinion if in his/her medical judgment discontinuation is in the best interest of the participant
- Sponsor request for safety reasons
- Any AE that is intolerable to the participant and that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the Investigator or Medical Monitor would lead to undue risk to the participant if dosing continued
- The participant experiences an SAE assessed as related to study treatment
- The participant tested positive for SARS-CoV-2 per polymerase chain reaction test or is suspected to have SARS-CoV-2 infection
- If the following liver test abnormalities develop, study treatment should be discontinued with appropriate clinical follow-up (including repeat laboratory tests, until a participant's laboratory profile has returned to normal/baseline status):
    - ALT or AST >8 × ULN or ALT or AST >5 × ULN for >2 weeks
    - ALT or AST >3 × ULN and TBL >2 × ULN or international normalized ratio >1.5
    - ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ECG findings of QTcF prolongation of [redacted], or a change of >60 ms from the pre-dose ECG, based on the average of triplicate ECGs
- Participants who experience suicidal ideation or attempt suicide
- Safety recommendation based on DMC / investigator/ Sponsor assessment of AEs and AESI
- If the participant becomes pregnant at any time after providing a signed ICF, the participant must be withdrawn immediately and if the participant has received at least 1 dose of experimental study treatment the participant must be followed through the pregnancy (refer to Appendix 5).
- If the participant undergoes urgent surgical procedures for endometriosis-related pain.
- The participant was erroneously included in the study (failed to meet protocol entry criteria)
- Participants whose treatment assignment has intentionally been unblinded by the Investigator
- The participant participates in another investigational study
- The participant is unable to comply with protocol requirements (eg, eDiary compliance, use of study treatment, use of rescue and prohibited medication, etc.)

Participants removed from study treatment for any reason will undergo the assessments for the discontinuation Visit (SoA, Section 1.3) and will have a Follow-up Visit to assess safety after completing 1 full cycle after the participant's last dose of study treatment.

A participant will be considered "discontinued due to an AE" if she withdraws from the study due to any AE, regardless of whether or not the AE is considered related to study treatment. If the participant withdraws from the study due to an AE, the Investigator should arrange for the participant to be followed appropriately until the AE has resolved or stabilized (in the opinion of the Investigator).

Decisions about medical care after study treatment discontinuation will be made according to Investigator's opinion.

The Investigator will document the reason(s) for treatment or study discontinuation. The Medical Monitor should be informed when a participant is withdrawn from the study.

Participants who do not wish to conceive after the last dose of study treatment should begin a new contraceptive method as soon as possible. Post-study contraceptive counseling will be provided by study site personnel in accordance with the SoA (Section 1.3).

7.3 Criteria for Study Termination

The DMC will conduct periodic and ad hoc (urgent) reviews of the safety data during the course of the study. This evaluation includes the review of the AEs thought to be of major significance, as referred in Section 2.3.1 and Section 7.2. The DMC recommendation, which may include study termination, will be urgently evaluated by the Sponsor for decision. Please refer to the DMC Charter and Sections 2.3.1 and 7.2 in the protocol.

The Sponsor reserves the right to discontinue the entire study or stop the study at a site for safety or administrative reasons at any time. Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), drug safety problems, or at the discretion of the Sponsor. The Sponsor will promptly notify the Investigator and the Regulatory Authorities if the study is prematurely terminated, and the Investigator or designee must promptly notify the IRB/IEC and study participants and ensure that appropriate follow-up of the participants is conducted.

7.4 Lost to Follow-up

A participant 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 participant fails to return to the study site for a required study visit:

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, she will be considered to have withdrawn from the study.
- Study site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study treatment. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8.0 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants met all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 General Assessments

8.1.1 Inclusion and Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the Investigator or qualified designee at Screening to ensure that the participant qualifies for the study. At [redacted], recheck clinical status before randomization (eg, pain score, compliance with eDiary, study treatment compliance, and rescue medication, negative pregnancy test).

8.1.2 Participant Identification Card

The Investigator or qualified designee will provide the participant with an identification card immediately after the participant provides documented informed consent. The identification card will identify them as participants in the research study and will contain the study site contact information (including direct telephone numbers) to be used in the event of an emergency. At the time of Randomization Visit, the study site personnel will add the treatment number to the participant identification card.

8.1.3 Assignment of Participant Number

All participants who consent, will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to Randomization Visit. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Specific details are provided in Section 6.3.

8.1.4 Assignment of Treatment Number

All eligible participants will receive a treatment (allocation) number. Treatment numbers cannot be re-assigned to another participant. A single participant cannot be assigned >1 treatment number.

8.1.5 Demographics

Demographics and baseline characteristics include age, race, ethnicity (eg, Hispanic or Latin origin), body weight, height, body mass index (BMI) (kg/m^2), general medical history, and gynecological history.

For France, see Appendix 9 for collection of Race.

8.1.6 Medical History and Substance Use

A medical history, including medical history regarding HIV, illicit drugs, alcohol, and tobacco use will be obtained by the Investigator or qualified designee.

8.1.7 Gynecological History

A gynecological history (including menstrual history) will be obtained by the investigator or qualified designee for all participants. Special attention should be given to the gynecologic-related inclusion (eg, surgical confirmation of endometriosis, history of pelvic pain, characteristics of participant's menstrual cycle, etc.) and exclusion criteria (Section 5.2).

As part of the gynecological history and to ensure the participant is eligible for study participation, the investigator or qualified designee will confirm that the participant has cyclic (DYS) AND non-menstrual, moderate to severe endometriosis-related pelvic pain, using an NRS (0-10 anchored with 0 [no pain] and 10 [extremely severe pain]).

Pregnancy history (including gravidity and parity), including number of previous pregnancies and number of live births should be collected for all participants at V1 and reported on the appropriate eCRF.

8.1.8 Urinalysis

Urine samples will be collected at Screening. Protein, pH, glucose, blood, ketones, bilirubin, urobilinogen, nitrite, and leucocytes will be evaluated.

8.1.9 Prior and Concomitant Medications

8.1.9.1 Prior Medications

The Investigator or qualified designee will review current medication use at the time of Screening and prior medication use, as applicable based on the time of screening in relation to planned Randomization Visit.

The medication review should specifically address any treatment that would meet the protocol-specified requirement for prohibited medications (Section 6.8.2).

8.1.9.2 Concomitant Medications

The Investigator or qualified designee will record medication, if any, taken by the participant during the study. Concomitant medications should be reviewed at every study visit or contact. The use of herbal supplements and nonprescription medications should be recorded as concomitant medications. Please refer to Section 6.8 for further details.

8.2 Efficacy and Quality of Life Assessments

CCI

8.2.1 Electronic Diary Dispensing and Instructions

At CC, each participant will be given an eDiary and will be properly trained and instructed on its use by the investigator or qualified designee.

Participants will have the option to use their own personal device for collection of PROs if they would not like a separate device provided to them. CCI diary is to be completed on a downloaded app which will be detailed in enhanced Clinical Outcome Assessment manual. Participants should bring their eDiary device for all study visits and should be contacted and reminded to do so (eg, by phone or text) before each visit.

CCI

must be completed CCI and if forgotten the recollection period is only 24 hours. Preferably, this will be done at the same time each day (eg, before bedtime). Participants will be instructed to enter the CCI eDiary information in accordance with the SoA (Section 1.3). The eDiary is equipped with a sound alert to CCI remind participants to complete the eDiary. Reminders will be sent to the participants in the evening if their CCI eDiary has not been completed for the previous day.

Participants will be instructed to complete the CCI at the beginning of their corresponding site visit for visits indicated in the SoA (Section 1.3). On the day of these visits, the CCI eDiary be completed at the same time as other days.

The ePRO instruments have to be completed by the participants themselves, with no external help.

It is estimated that completion of the CCI questions in the eDiary will take approximately 5 minutes.

If a participant discontinues early from study intervention but agrees to be followed for the remaining study visits, she will be asked to continue completing the CCI eDiary entries.

Additional information for the site staff can be found on a secure online portal. Additional information for the participants can be found in the participants manual. Participants will complete the efficacy assessments in the order presented below and in accordance with the SoA (Section 1.3):

- eDiary (to be completed CCI):

CCI

At the study site visit, the participant must complete all eDiary assessments prior to any evaluation conducted by study site staff and/or the Investigator.

8.2.2 CCI eDiary

The eDiary[57] will be completed as indicated in the SoA (Section 1.3).

CCI [redacted]

Participants will complete eDiary items CCI [redacted]

CCI [redacted]

CCI [redacted]

Participants will complete eDiary items CCI [redacted]. The NRS measures the level of interference 0 (not difficult) to 10 (extremely difficult) where lower value represents a better outcome. An interference score is obtained each day.

8.2.2.3 Rescue Medication Use

Participants will be asked daily whether they used the rescue medication in the past 24 hours to treat their ERP. CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

8.3 Safety Assessments

All safety assessments will be performed at the times indicated in the SoA (Section 1.3). Details regarding specific safety procedures/assessments to be performed in this study are provided below.

8.3.1 Physical Examinations

Complete physical examinations will be performed at the times indicated in the SoA (Section 1.3). These examinations will include participant's general appearance, head, eyes, ears, nose, throat, neck/thyroid, heart, lungs, musculoskeletal system, gastrointestinal system, neurological system, and skin. Special attention should be taken during screening to exclude any other pelvic pain conditions by performing an extensive anamnesis.

A focused physical examination (palpation and auscultation, if applicable) will be performed consistent with local requirements at the times indicated in the SoA (Section 1.3)

The participant's body weight and height will be recorded at the times indicated in the SoA (Section 1.3) and BMI will be calculated.

Clinically significant findings prior to dosing will be recorded on the medical history eCRF.

During the study, any clinically significant change from BC will be recorded as an AE on the AE eCRF. Clinical significance is defined as any variation in physical findings that has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the participant until the finding is resolved or, in the judgment of the Investigator, follow-up is no longer medically necessary.

A clinical breast examination and a gynecological examination including a pelvic exam will be performed at the times indicated in the SoA (Section 1.3).

8.3.2 Vital Signs

Vital signs include assessment of heart rate, respiratory rate, body temperature (aural measurement), and BP. Vital signs will be taken with the participant in the supine position after resting for at least 5 minutes, at the times indicated in the SoA (Section 1.3).

8.3.3 Electrocardiograms

Triplicate standard 12-lead ECGs will be obtained after the participant has been in a supine position for at least 5 minutes at times indicated in the SoA (Section 1.3). The ECGs will be

measured using standardized equipment provided by a central core laboratory. The ECGs will be assessed by central review and a report provided to the site. Results from Screening ECG must be either normal or reveal findings deemed not to be of clinical significance by the Investigator for the participant to qualify for the study. CCI [redacted]

8.3.4 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a standardized clinician-reported outcome tool used to assess suicidal risk status of the participant that can be administered by trained non-mental health personnel. The assessment is completed based on participant responses. The C-SSRS should be completed before other types of study procedures, such as blood draws and physical examinations, are performed. Suicidality will be monitored throughout the study employing a validated questionnaire C-SSRS. The C-SSRS will be completed at each site visit as indicated in the SoA (Section 1.3) and the results must be evaluated by the Investigator to recommend any additional intervention, if needed. Based on determination of positive C-SSRS results for suicidality, the participants will be discontinued from the study medication and referred to a specialist at the Investigator's discretion for further evaluation. CCI [redacted]

CCI [redacted]

CCI

8.3.7 Clinical Safety Laboratory Tests

CCI , clinical chemistry, urinalysis, serology, and additional laboratory parameters to be tested during the study are listed in Appendix 3. At Screening and the EOS Visit, participants are required to be in a fasted state at the time of the laboratory sample (with fasting defined as at least 8 hours following the last meal or snack). At all other scheduled visits, participants do not need to be in a fasted state; however, fasting status will be documented. At least 1 backup aliquot at each visit will be stored for potential further assessments.

Laboratory samples will be analyzed by a central laboratory. Laboratory tests may be repeated at any visit if there was an abnormal finding at the most recent previous evaluation or if additional information is clinically necessary to appropriately evaluate the participant's current condition, follow-up, and/or manage an AE.

The Investigator will review laboratory results with a frequency that ensures participants safety. Clinically significant changes from Screening in laboratory results must be considered

an AE and recorded in the eCRF. Clinical significance is defined as any variation in a laboratory result that has medical relevance and that results in a change in medical care. The Investigator will continue to monitor the participant until the finding is resolved or, in the judgment of the Investigator, follow-up is no longer medically necessary.

Local assessment of clinical laboratory parameters is permitted when these data are required for safety reasons in a timeframe faster than the central laboratory can provide.

Specific withdrawal criteria for liver enzymes are presented in the Withdrawal Section 7.0.

8.3.7.1 Papanicolaou Test

If a previous PAP smear report is available and the results meet the local guidelines, no additional tests are needed. If additional PAP smear or equivalent cervical cytology in combination with HPV testing are required, they will be performed at site, following the local guidelines at Visit 1.

If the results of the PAP smear are abnormal the participant will be informed of the results and advised as to any medically appropriate follow-up. A participant would be excluded if the participant has any of the following cervical pathology: atypical squamous cells ASC-H, low-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion, atypical glandular cells [any type], squamous cell carcinoma, or adenocarcinoma [in situ or invasive]) or has a high-risk HPV.

8.3.7.2 Sexually Transmitted Infection Panel

The STI panel will be performed, if indicated and participants will be tested for gonorrhea and chlamydia unless they were screened within the past 3 months and have no new sexual partner. Testing for trichomonas and bacterial vaginosis will only be required if abnormal vaginal discharge is present. Testing will be performed locally at Visit 1 and may be repeated during the study as needed.

8.3.7.3 Serum Hormone Tests

CCI

[redacted]

CCI

[redacted]

8.3.8 Pregnancy Testing

Women of childbearing potential should only be included after a confirmed menstrual period and a negative highly sensitive urine/serum pregnancy test.

Additional pregnancy testing should be performed at times specified during the treatment period and at safety follow-up, corresponding to protocol-defined time frame in Section 5.1 after the last dose of study treatment and as required locally.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

CCI

[redacted]

8.4 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE and SAE can be found in Appendix 4.

Adverse events and SAEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of AEs and SAEs. Investigators remain responsible for following up AEs and SAEs for outcome according to Section 8.4.3. Investigators remain

responsible for following up events that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment or study procedures, or that caused the participant to discontinue the study treatment or withdraw from the study (see Section 7.0).

The Investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE with respect to seriousness, severity, and causality.

For any guidance regarding AE/SAE reporting, the Investigator should contact the Medical Monitor.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

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

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of the Investigator's awareness of the event, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of their awareness of the updated information.

From the time of screening (V1) through EOS/discontinuation, which is 30 days after last intake of study treatment, all AEs, SAEs, and other reportable safety events must be reported by the Investigator.

Additionally, any SAE brought to the attention of an Investigator at any time outside the period specified in the previous paragraph must be reported immediately (within 24 hours of learning about the event) to the Sponsor if the event is considered related to study treatment.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discontinued from the study, the event/cause of death is considered to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor or designee.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 7.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

Table 7 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Screening (V1) to Pre-Treatment Allocation (C)	Reporting Time Period: Treatment Allocation (C) through Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
Nonserious Adverse Event (NSAE)	Report if: • Due to protocol-specified procedure • Causes exclusion	Report all	Per data entry guidelines
Serious Adverse Event (SAE)	Report if: • Due to protocol-specified procedure • Causes exclusion	Report all	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: • Participant has been exposed to any protocol-specified procedure	Report all	Within 24 hours of learning of event
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Overdose	Report if: • receiving CCI or other CCI medication (including Rescue Medication)	Report all	All overdose events associated with SAE (including intentional suicidal/self-harming intent) must be reported within 24 hours by completing a SAE form Overdose events associated with a non-serious AE must be reported within 5 calendar days of learning of event All other overdose cases not associated with AE/SAE must be captured in the appropriate section of eCRF

8.4.2 Method of Detecting AEs and SAEs

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

8.4.3 Follow-up of AEs, AESIs, and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy complications/outcomes (Appendix 4) and exposure during breastfeeding, and AESIs, must be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). In addition, the Investigator will make every attempt to follow all nonserious AEs that occur in eligible (allocated to treatment) participants for outcome. Further information on follow-up procedures is given in Appendix 4.

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment 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 treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the corresponding regulatory authority, IRB/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. When an investigator receives a SUSAR, it should be reported to the IRB/IEC immediately or within 24 hours.
- SUSAR reports will be submitted electronically (gateway to gateway) from the sponsor's safety database to the EudraVigilance Clinical Trial Module, in accordance with the EU Clinical Trial Regulation.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy

If any participant becomes pregnant during the study, the study site must discontinue the participant from the study treatment immediately and have her return for an early-study termination visit. The Investigator must inform the participant of her right to receive treatment information. If the participant chooses to receive unblinded treatment information, the individual blind should be broken, and the treatment assignment provided to the participant. The study team will remain blinded to the participant's treatment assignment.

If the participant agrees, the Investigator should notify the participant's primary care physician of the pregnancy and provide details of the participant's participation in the study and treatment

(blinded or unblinded, as applicable).

- Details of all pregnancies will be collected based on the schedule outlined in Appendix 5.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 and Appendix 5.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.6 Adverse Events of Special Interest

Selected adverse events (nonserious and serious) that might be potential precursors or prodromes for more serious medical conditions will be considered as AESIs for this protocol. All AESIs must be reported as AEs in the eCRF.

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8.5 Pharmacokinetics

8.5.1 Collection of Samples

Samples for determination of OG-6219 and its primary, active metabolite FOR-1011 concentration will be collected for all participants as per the SoA in Section 1.3 and in Table 8.

Samples of approximately 2 mL of blood will be collected at each PK timepoints for measurement of plasma concentrations of OG-6219 and FOR-1011. Instructions for the collection, handling, storage, and shipment of biological samples (plasma) will be provided separately in a laboratory manual by the Sponsor or its designee. The actual date and time (24-hour clock time) of each sample will be recorded. The time and date of each study treatment administration on the visit days will be recorded for all participants.

Samples will be used to evaluate the PK of OG-6219 and FOR-1011. Each timepoints for PK will yield one primary and one backup sample. Samples collected for analyses of OG-6219 and FOR-1011 (plasma) concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study and/or for modeling and simulation of

exposure and/or exposure versus response.

Table 8 Schedule of Pharmacokinetics Sampling

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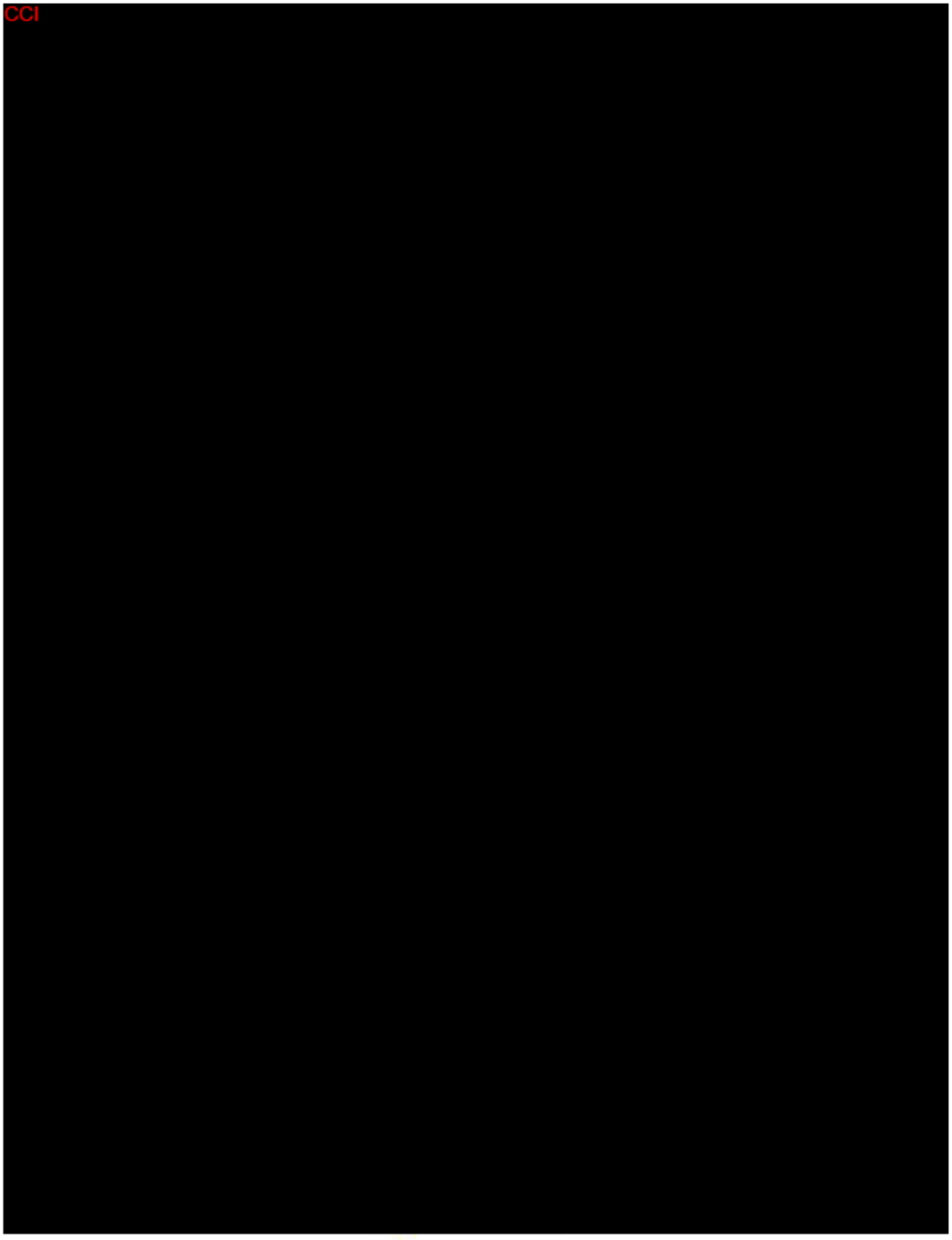

CCI [redacted]

8.5.2 Determination of Drug Concentration

Samples for the determination of OG-6219 and FOR-1011 in plasma will be analyzed using an appropriate validated bioanalytical method. Full details of the bioanalytical method will be described in a separate Bioanalytical Report.

All samples still within the known stability of the analyte of interest at the time of receipt by the bioanalytical laboratory will be analyzed.

Remaining plasma samples may be participated to further analysis by the Sponsor or designee for the purpose of development of additional bioanalytical assays and/or for metabolite analysis in human plasma.

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

Any unexpected below the limit of quantification must be timely reported to the Sponsor or its delegate.

8.6 Pharmacodynamics

Blood samples for PD will be collected for all participants as per the SoA in Section 1.3. Instructions for the collection, handling, storage, and shipment of biological samples will be provided separately in a laboratory manual by the Sponsor or designee.

The PD/Safety assessment of CCI [redacted] will be determined at the times indicated in the SoA (Section 1.3).

CCI [redacted]

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

CCI [redacted]

For the CCI [redacted], blood specimens will be collected as per the times indicated in the SoA (Section 1.3).

8.9 Health Economics/Medical Resource Utilization and Health Economics

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

8.10 Changes to Study Procedures Due to Exceptional circumstances

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the Investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the Sponsor's written approval, sites may implement changes if permitted by local regulations.

COVID-19

The following information provides guidance regarding changes to the study procedures that could be implemented for study participants or study sites affected by the COVID-19 public health emergency. This guidance takes references from the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency–Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, updated 03 June 2020, and the European Medicines Agency Guidance on the Management of Clinical Trials During the COVID-19 Pandemic, Version 3 (28 April 2020).

As the COVID-19 pandemic may peak in different regions at different times and restrictions implemented by local laws and recommendations may vary, any decision on participation and procedural changes should be made on a case-by-case basis by the Investigator in consultation with the study team and the medical team as needed, while maintaining participant safety and confidentiality as the priority.

Procedural changes due to COVID-19 may include the following:

- Participants must be fully vaccinated with approved COVID-19 vaccines as per the country-specific requirements.
- Missed study site visits or participant withdrawals due to COVID-19 must be recorded on the eCRF. Participants who discontinued from Screening or CCI due to COVID-19-related factors but were otherwise qualified to participate in the study may be rescreened (see Appendix 2). Any rescreening must be approved by Medical Monitor.
- Allow electronic clinical outcomes assessments typically scheduled for completion at the study site to be completed at home if a study site visit cannot occur.
- In specific circumstances and with Sponsor approval, it may be allowed to transfer the participants to study sites away from the risk zones or closer to their homes (either to new study sites or sites already participating in the study).

Deviations from the protocol-specified procedures (eg, laboratory assessments) will be recorded as related to COVID-19.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

CCI [redacted]

Where appropriate, variables will be summarized descriptively (frequency and percent will be summarized for categorical variables; n, mean, standard deviation [SD], median, minimum, and maximum will be presented for continuous variables) by study time point (cycle or visit) and by treatment group.

9.1.1 Multiplicity Adjustment

No adjustment for multiplicity is planned since this is a Phase 2a/b study; the comparisons of interest are for each active dose group versus control. Secondary, and exploratory endpoints will thus be tested at CCI [redacted] and nominal p-values will be provided.

9.2 Analysis Sets

- Full Analysis Set (FAS)–all participants randomized
- Modified Full Analysis Set (MFAS)–all participants randomized who receive at least 1 dose of study treatment and who completed at least 1 subsequent diary entry CCI [redacted]
- Per Protocol (PP)–all participants in the MFAS who completed at least one treatment cycle with no major protocol deviations that may impact the interpretation of the primary efficacy endpoint
- Safety (SAF)–all participants who received at least 1 dose of study treatment
- Safety Follow-up Analysis Set (SFAS)–all participants randomized who receive at least 1 dose of study treatment and have at least 1 diary entry CCI [redacted] after the date of last treatment
- PK Analysis Set: The PK analysis set is a subset of the Safety analysis set (SAF) and will include all participants who received at least a dose of OG-6219 and have at least 1 quantifiable OG-6219 or FOR-1011 concentration.
- Pharmacokinetic Analysis Set for Noncompartmental Analysis: The PK analysis set for noncompartmental analysis (NCA) will include all participants in the PK analysis set CCI chose intensive PK sampling CCI [redacted] and have sufficient samples to determine at least one PK parameter for OG-6219 or FOR-1011. Intensive PK sampling is optional where a separate consent would be provided.
- PD Analysis Set–The PD analysis set is a subset of the SAF and will include all participants who received at least a dose of OG-6219 or Placebo and have at least 1 quantifiable PD endpoint without protocol deviations or events affecting the PD results.

Analyses will be performed in the respective analysis populations (safety analyses in the safety set, PK analysis in the PK analysis set and PK analysis Set for NCA, PD analysis in the PD analysis set, and efficacy analyses in the MFAS for on-treatment efficacy, SFAS for post-treatment efficacy, and select efficacy analyses in the FAS and/or PP analysis set).

9.3 Sample Size Considerations

Approximately CCI pre-menopausal females aged 18 to 49 years old (inclusive), who have been surgically diagnosed with endometriosis within the last 4 months to 10 years prior to V1, will be screened to achieve 380 randomly assigned to the study treatment (C participants in each group). A total of 380 participants will provide CCI power to detect a difference CCI between an OG-6219 dose group and Placebo in change from baseline to TRC3 of mean OPP, assuming a common SD of 2.2. This power calculation is based on a CCI and a dropout rate of CCI.

A minimum subset of C participants per group CCI will be enrolled for optional intensive PK sampling for the entire duration of the study.

9.4 Statistical Analyses

9.4.1 General Considerations

The SAP will be developed and finalized before database lock and will describe the participant analysis sets used for each analysis, methods of analysis, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary, and exploratory endpoints.

All statistical models will evaluate pairwise treatment comparisons between Placebo and a single OG-6219 dose arm. No comparisons will be made between different dose levels.

All data will be listed, and summary tables using descriptive statistics over time will be provided. Summary statistics will be presented by treatment group.

9.4.2 Primary Endpoint Analysis

The primary endpoint will be the mean change from BC of the average daily OPP score during TRC3. The OPP will be calculated for each cycle as the total of OPP scores reported during the cycle divided by the number of days during the cycle in which the score was reported. For participants who discontinue early, their last cycle will be associated with the cycle number at entry into the cycle. The primary analysis will be conducted using the MFAS and will use a longitudinal model. The response vector for the model will be change from BC in the average OPP during TRC1, TRC2, and TRC3. Model terms will include the respective baseline, treatment, time (ie, cycle), and treatment-time interaction, allowing for the inclusion of individual outcomes over time (cycle). An unstructured error structure will be assumed. If

nonconvergence is encountered, compound symmetry (CS) and first-order autoregressive AR(1) error structures will be considered.

Least squares mean change from baseline for each treatment group, with corresponding standard errors will be provided. Estimated treatment differences (each active treatment group versus Placebo) with corresponding 95% CI and 2-sided p-values will also be provided for each active treatment group. No missing data will be imputed for the primary analysis.

Supportive analyses will be conducted using an analysis of covariance (ANCOVA) on the change from baseline to the TRC3, with treatment as a fixed factor and baseline OPP as a covariate.

The primary longitudinal and ANCOVA models will be repeated using the PP set.

A completers analysis will be performed for those participants who completed all 3 treatment cycles. Details regarding additional sensitivity and subgroup analyses of the primary efficacy endpoint will be described in the SAP.

9.4.3 Secondary Endpoint Analysis

Secondary endpoints assessing change in continuous endpoints over time (either measurements within the cycle or at an individual visit) will use longitudinal models as described for the primary endpoint and/or ANCOVA models. Changes from SC to SFC will be compared using ANCOVA models in the SFAS. Select longitudinal models which focus on TRC1 and TRC2 may exclude TRC3 from the model. An unstructured error structure will be assumed for all longitudinal models. If nonconvergence is encountered, CS and AR (1) error structures will be considered.

Definitions corresponding to the incidence of clinically significant values will be provided in the SAP.

9.4.4 Exploratory Endpoint Analysis

Exploratory endpoints will be evaluated in the same manner as secondary continuous endpoints.

9.4.5 Pharmacokinetic Analyses

The OG-6219 and its primary metabolite FOR-1011 concentrations (all participants receiving OG-6219) will be listed and summarized by treatment, study visit, and scheduled time for the PK analysis set, as appropriate.

9.4.5.1 Noncompartmental Pharmacokinetic Analyses

PK analyses may be performed on the PK Analysis Set for NCA. Plasma-concentration time data for OG-6219 and FOR-1011 will be summarized by visit and time using descriptive statistics.

Plasma-concentration data of OG-6219 and FOR-1011 will be analyzed for the PK analysis set for NCA using standard noncompartmental methods. The following PK parameters will be calculated when possible: AUC_{tau}, C_{max}, and t_{max}. Additional details of the PK analysis will be described in the SAP. The PK parameters of OG-6219 and FOR-1011 will be listed for each participant and summarized using descriptive statistics.

9.4.6 Pharmacodynamic Analyses

The PD endpoints for CCI [redacted] levels will be compared versus Placebo at CCI [redacted]. The CC blood collection needs to occur prior to dosing of study medication. In addition, the levels of these PD parameters will be compared at CC versus CC.

The results of these PD endpoints will be summarized by treatment and time.

9.4.7 Safety Analyses

The SAF will be used for all safety analysis.

Baseline will be defined as the last measurement before study treatment intake. Scheduled assessments on the date of randomization will be considered pre-treatment for the definition of baseline.

9.4.7.1 Adverse Events

Adverse events will be coded using the most current version of Medical Dictionary for Regulatory Activities. All AEs, including those that are not treatment-emergent, will be listed. A TEAE is defined as an AE that is new or worsened in severity after the first dose of study treatment, including those events which begin during Safety Follow-up; events starting on the day of first dose will be considered treatment-emergent unless information is available to indicate the event started prior to the time of first dose. The timeframe for a TEAE after stopping the randomized treatment is 14 days. Treatment-emergent AEs will be summarized by system organ class, preferred term (PT), and treatment. Summaries by treatment group will be prepared for all AEs, TEAEs, and SAEs. A summary of TEAEs by severity will also be presented.

For summary tables, AEs coded to the same PT will be counted only once within a given participant. If an AE was recorded on multiple occasions in the same treatment period, only the highest severity and the highest degree of relationship to the study treatment will be

presented. If 2 or more clinical events were reported within a single AE entry, then the corresponding individual PT will be coded separately.

9.4.7.2 Vital Sign Assessments

Results of vital sign parameters (including weight and BMI) and changes from baseline will be summarized descriptively. Results will also be listed by participant.

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9.4.7.4 Prior and Concomitant Medications

Prior and concomitant medications will be listed by participant, coded using the WHO Drug Dictionary, and summarized descriptively. Prior medications are defined as any medications started prior to the day of the first dose of study treatment. Concomitant medications are defined as any medications taken on the day of or after the first dose of study treatment. Medications will be classified according to primary fourth level Anatomical Therapeutic Chemical codes and WHO Drug preferred names in the listing. Participants may have >1 concomitant treatment per drug class and per preferred name. Summary tables will be generated by treatment for both prior and concomitant treatments, and in the tabular summaries, a participant will be counted only once for a given prior or concomitant treatment.

9.4.8 Other Analyses

9.4.8.1 Demographics, Baseline Characteristics, and Disposition

Demographics and baseline characteristics include age, race, ethnicity (Hispanic or Latin origin), body weight, height, BMI (kg/m^2), general medical history, and gynecological history.

All variables will be summarized by treatment group using descriptive statistics. Demographics and baseline characteristics will be summarized for the SAF, FAS, and MFAS.

The number and percentage (as applicable) of participants screened and randomized to study treatment, the primary reason for screening failure, and the primary reason for discontinuation from study treatment will be displayed. In addition, the primary reason why participants were randomized to study treatment but discontinued prior to study treatment (non-treated participants) will be presented in a table.

The number of participants who were treated and who completed the clinical study will also be tabulated. A disposition graph of participants will be provided.

The number of participants with protocol deviations will be tabulated by deviation for the FAS. In addition, all deviations will be listed by participant.

9.5 Interim Analysis

There will be no interim analysis [redacted].
An interim psychometric analysis using blinded data will be performed to affirm methods for establishing pain responder cutoffs.

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11.0 APPENDIX

Appendix 1 Abbreviations

Abbreviation	Definition
CCI [redacted]	[redacted]
ADL	Activities of Daily Living
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ANCOVA	analysis of covariance
AR (1)	first-order autoregressive 1
AST	Aspartate aminotransferase
AUC_{tau}	Area under the plasma-concentration-time curve during a dosing interval, calculated by linear up/log down trapezoidal summation
BC	Baseline Cycle
BCRP	Breast Cancer Resistance Protein
BID	Twice a day
BMI	Body mass index
BP	Blood pressure
CCI [redacted]	[redacted]
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum concentration, obtained directly from the observed concentration versus time data
COC	Combined oral contraceptives
COVID-19	Coronavirus Disease 2019
COX-2	Cyclooxygenase-2
CRO	Contract Research Organization
CS	compound symmetry
C-SSRS	Columbia-Suicide Severity Rating Scale
CCI [redacted]	[redacted]

Abbreviation	Definition
CYP	Cytochrome
CCI	[redacted]
DMC	Data Monitoring Committee
DX	Day X
DYS	Dysmenorrhea
E1	Estrone
E2	Estradiol
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
ePRO	Electronic Patient-reported outcome
EHP-30	Endometriosis Health Profile-30
EOS	End of Study
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome
EQ-VAS	EQ Visual Analog Scale
CCI [redacted]	[redacted]
ER	Estrogen receptor
ERP	Endometriosis-related pain
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
CCI	[redacted]
GCP	Good Clinical Practice
GI	Gastrointestinal
GnRH	Gonadotropin releasing hormone
hCG	Human chorionic gonadotropin
hERG	Human Ether-à-go-go-Related Gene
HIV	Human immunodeficiency virus

Abbreviation	Definition
HPG	Hypothalamic pituitary gonadal
HPV	Human papillomavirus
HRT	Hormonal replacement therapy
HSD17β1	Hydroxysteroid-17β-dehydrogenase type 1
HSD17β2	Hydroxysteroid-17β-dehydrogenases 2
HSD17β5	Hydroxysteroid-17β-dehydrogenases 5
HSD17βs	Hydroxysteroid-17β-dehydrogenases
IA	Interim Analysis
IB	Investigator's Brochure
IC50	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
CC	[redacted]
MCH	Mean corpuscular hemoglobin
MCHC	Mean cell hemoglobin concentration
MCV	Mean corpuscular volume
MFAS	Modified Full Analysis Set
MRI	Magnetic Resonance Imaging
NCA	Noncompartmental analysis
NMPP	Non-menstrual pelvic pain
NRS	Numeric rating scale
NSAID	Nonsteroidal anti-inflammatory drug
CCI	[redacted]
OPP	Overall Pelvic Pain (endometriosis-related)
OTC	Over the counter
CCI	[redacted]

Abbreviation	Definition
PD	Pharmacodynamic
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
P-gp	P-Glycoprotein
PK	Pharmacokinetic
PoC	Proof of Concept
CCI	[redacted]
PRO	Patient-reported outcome
PT	Preferred term
QTcF	QT interval will be assessed using the CCI
QTL	Quality tolerance limit
RDW	Red Cell Distribution Width
SAE	Serious Adverse Event
CCI	[redacted]
SARS-CoV-2	Severe acute respiratory syndrome–related coronavirus-2
SC	Screening Cycle
SD	Standard deviation
SDR	Short-chain dehydrogenase/reductase
SFC	Safety Follow-up Cycle
CCI	[redacted]
SoA	Schedule of Activities
STI	Sexually transmitted infection
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
T_{max}	Time taken to reach the maximum concentration
CCI	[redacted]
TRC1	Treatment Cycle 1
TRC2	Treatment Cycle 2
TRC3	Treatment Cycle 3

Abbreviation	Definition
CCI [redacted]	
ULN	Upper limit of normal
UPT	Urine Pregnancy Test
UV	Ultraviolet
VAS	Visual Analog Scale
VX	Visit X
WOCBP	Women of childbearing potential
CCI [redacted]	[redacted]
β-hCG	β-human chorionic gonadotropin

Term	Definition
Screening Period	• One SC: Starts at C (first day of the menses) and ends one-day before next menses. • One BC during the single-blind, CCI [redacted] period: Starts at C (first day of the menses) and ends at one-day before next menses.
Randomization	C, this is on first day of the next menses after the end of BC.
Treatment Period	Three treatment cycles (TRC1, TRC2, and TRC3) after V4: • TRC1 is the period between the first day of menses associated with treatment start (C) to the day prior to the first day of next menses, regardless of number of days. CCI [redacted] is dependent on confirmation of urine CCI [redacted] plus CCI [redacted]. • TRC2 is the period between the first day of second menses after end of BC to the day prior to first day of next menses, regardless of number of days. Phone Contact 1 is done during the menses. • TRC3 or EOT is the period between the first day of third menses after end of BC to either end after 3 completed cycles or CCI [redacted] on study treatment, whichever occurs first.
Safety Follow-up	• SFC, is the period of time between the first day after stopping study treatment during TRC3 and ends after 30 consecutive days (regardless of whether it aligns with first day menses or not). Phone contact 2 is done at Day 14 after last intake of study treatment. CCI [redacted] at the first day of next menses is considered End of Study (EOS).

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable ICH/GCP Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to the participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

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 SAEs, or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the study site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, EU CTR 536/2014 for clinical studies and all other applicable local regulations.

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative. The study will not start at any study site at which the Investigator has not signed the protocol.

Adequate Resources

The Investigator is responsible for supervising any individual or party to whom the Investigator delegates study-related duties and functions conducted at the study site.

If the Investigator/institution retains the services of any individual or party to perform study-related duties and functions, the Investigator/institution should ensure this individual, or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested 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.

Insurance

The Sponsor has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines, whichever is applicable. The terms of the insurance will be kept in the study files.

Recruitment and Informed Consent Process

Trial participants will be identified from existing patient lists of the Investigators involved in the trial. Investigators may be supported with physician referral or direct to patient outreach (local or centralised advertisement and trial awareness) to identify potential trial participants.

Potential Trial participants will be presented with trial information via the following:

- Printed or electronic study awareness materials to be provided by the site staff either in clinics or via post/email (patient brochure, poster, Banner ads)
- Study information and pre-screening website with educational video (storyboard)
- Social media advertisement (Clinical trial posts)
- Direct mail regarding the trial

Any trial-related information will be handed to a potential participant by a member of the clinical trial team at the trial site prior to consent and before any trial-related activities are performed.

The Investigator or medically qualified designee will explain the nature of the study to the participant or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection 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 participant 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.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

The Investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent, and assent if applicable, from each potential participant prior to participating in this clinical study.

Documentation of Informed Consent

Informed consent given by the participant must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant and of the person conducting the consent discussion.

A copy of the signed and dated ICF should be given to the participant before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature.

Specifics about the study and the study population are to be included in the study ICF.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

During a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative (if applicable) should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local laboratories), this verbal information given to the participant should be documented in the participant's source notes.

A separate consent for optional intensive PK analysis will be administered.

Participants who are rescreened are required to sign a new ICF if the rescreening is >42 days from the previous ICF signature date.

Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant 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 participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant 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.
- The contract between sponsor and study sites and any applicable third part involved in the trial specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

Committees Structure

Data Monitoring Committee

A DMC has been appointed for this study. The DMC is an external group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.

The monitoring process includes safety signal detection at any time during the study. This includes multiple safety evaluations by the DMC; the first evaluation is planned when approximately the first C participants randomized have either completed Phone Contact 1 or discontinued study treatment.

Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to any relevant database a summary of the results of the clinical study within 1 year from the end of the global clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

Data Quality Assurance

All relevant participant data relating to the study will be recorded on eCRFs. The laboratory data, eDiary, or other applicable data will be transmitted to the Sponsor or designee electronically. The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the data 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.

Quality tolerance limits (QTLs) will be pre-defined in the Monitoring Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of non-compliance 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 (eg, Contract Research Organizations [CROs]).

Records and documents, including signed ICFs, 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.

Details of study monitoring will be included in a separate Study Monitoring Plan.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study site's participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

Source documents provide evidence for the existence of the participant 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.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized study site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants 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.

Study and Study Site Termination

The Sponsor or 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:

For study termination:

- Discontinuation of further study treatment development.

For study site termination:

- 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 or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(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 participant and should assure appropriate participant therapy and/or follow-up.

Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study site will be set forth in the Clinical Trial Agreement.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 3 Clinical Laboratory Tests

The tests detailed in Table 9 will be performed by the central laboratory. Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the eCRF.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.0 of the protocol.

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

All study-required laboratory assessments will be performed by a central laboratory.

The results of each test must be entered into the eCRF. Investigators must document their review of each laboratory safety report.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations. Re-test of samples due to cancelled tests is permitted.

Table 9 Protocol-required Safety Laboratory Tests

Laboratory Assessments	Parameters	
Hematology	Platelet count	White blood cell count with differential (% and absolute):
	Red blood cell count	Neutrophils
	Hemoglobin	Lymphocytes
	Hematocrit	Monocytes
	CCI [redacted]	Peripheral smear
	Red blood cell indices:	Eosinophils
	Mean corpuscular volume (MCV)	Basophils
	Mean corpuscular hemoglobin (MCH)	
	Mean cell hemoglobin concentration (MCHC)	Coagulation tests
		Prothrombin time
	Red Cell Distribution Width (RDW)	Activated partial thromboplastin time
		Antithrombin III
	%Reticulocytes	

Laboratory Assessments	Parameters	
Clinical Chemistry[b]	Blood urea nitrogen (BUN)	Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase
	Creatinine	Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase
	Glucose (Fasting)	Alkaline phosphatase (ALP)
	Gamma glutamyl transferase (GGT)	Creatine kinase
	Urea	Creatine kinase MB fraction will be performed if clinically indicated
	Magnesium	Chloride
	Cholesterol	Globulin
	Potassium	Amylase
	Sodium	Total bilirubin
	Calcium	Conjugated and unconjugated bilirubin
	Lactate dehydrogenase (LDH)	Total protein
	Albumin	Phosphate
	Uric acid	Potassium
	C-reactive protein	Carbon dioxide (bicarbonate)
Urinalysis	Leucocytes	Red blood cells
	Protein	pH
	Bilirubin	Nitrite
	Urobilinogen	Specific gravity
	Ketones	Glucose
	Microscopy Hemoglobin	
Viral serology	Human immunodeficiency virus (HIV) I and II	Hepatitis C virus
	Hepatitis B Virus	Hepatitis A
	COVID-19 Virus and antibodies (following local guidelines)	
Other tests	Lipids: Total cholesterol, Low density lipoprotein cholesterol, High density lipoprotein cholesterol, and Triglycerides	
	CCI [redacted]	
	Sexually transmitted infection (STI) panel, papanicolaou (PAP) smear, human papillomavirus (HPV) testing (if required), transvaginal ultrasound (TVUS), endometrial biopsy (optional unless abnormal vaginal bleeding - at the discretion of the Investigator)	

Laboratory Assessments	Parameters
	Pregnancy: β-human chorionic gonadotropin (β–hCG), Urine pregnancy test (human chorionic gonadotropin)[c]
	CCI [redacted]
	The results of each test must be entered into the eCRF.

NOTES:
CCI [redacted]

[b] All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

[c] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

Appendix 4 AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting for Study Intervention

Definition of AE

AE Definition
An AE is any untoward medical occurrence in a clinical study participant administered an investigational product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related by the Investigator.

AESI Definition
Adverse events of special interest are any events identified for intensive review during the study. An AESI is a potential AE of scientific and medical interest specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified, or removed during a study by protocol amendment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or severity of the condition. • New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. All overdose events must be reported in accordance with its seriousness including overdose taken with intentional suicidal/ self-harming intent.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant'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 participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (eg, surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE. • 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.

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 (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:
a. Results in death • For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.
b. Is life-threatening • The term *life-threatening* in the definition of *serious* refers to an event in which the participant 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 participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment 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 treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant 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 (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- The term congenital anomaly/birth defect means there is suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

f. Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant 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 treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor or designee in lieu of completion of the applicable/required report form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

The severity of an AE is an estimate of the relative severity of the event made by the Investigator based on his or her clinical experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study treatment and each occurrence of each AE/SAE. The AE must be characterized as unrelated, unlikely to be related, possibly related, probably related, or unknown (unable to judge).
    - "Probably related" conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
    - "Possibly related" suggests that the association of the AE with the study treatment is unknown; however, the AE is not reasonably supported by other conditions.
    - "Unlikely to be related" suggests that only a remote connection exists between the study treatment and the AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant therapy, appear to explain the reported AE.
    - "Unrelated" is used if there is not a reasonable possibility that the study treatment caused the AE.
    - All efforts should be made to classify the AE according to the above categories. The category "unknown" (unable to judge) may be used only if the causality is not assessable, eg, because of insufficient evidence, conflicting evidence, conflicting data, or poor documentation.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to the study treatment administration will be considered and investigated.
- The Investigator will also consult the IB in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that 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 the Sponsor.

- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- 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 or designee 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.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of the Investigator's awareness of the information.

Reporting of SAEs

SAE Reporting to the Sponsor or Designee via an Electronic Data Collection System

- The primary mechanism for reporting an SAE to the Sponsor or designee will be the electronic data collection system. The study site will enter the event into the electronic data collection system within 24 hours of the Investigator's awareness of the event.
- If the electronic system is unavailable, then the study site will use the paper SAE report form (see next section) to report the event and will enter the event into the electronic data collection system as soon as the system becomes available.
- After the study is completed at a given study site, the electronic data collection system will be taken offline to prevent the entry of new data or changes to existing data.
- If a study site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection system has been taken offline, then the study site can report this information on a paper SAE report form (see next section) to the Sponsor or designee.
- Contacts for SAE reporting can be found in study manual, Investigator Study File Binder, or equivalent.

SAE Reporting to the Sponsor or Designee via Paper SAE Report Form
• Email transmission of the SAE form should be done in case there are technical issues with the electronic data capture system and SAE cannot be reported within 24 hours of awareness per the ICH guidelines via electronic data capture. The SAE/Pregnancy form should be emailed to the IQVIA safety project mailbox detailed in the form. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in study manual, Investigator Study File Binder, or equivalent.

Appendix 5 Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Pre-menopausal female with 1 of the following:
    a) Documented hysterectomy.
    b) Documented bilateral salpingectomy.
    c) Documented bilateral oophorectomy.

NOTE: Documentation can come from the study site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Post-menopausal female:
    a) A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrolment.

Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use adequate non-hormonal contraceptive methods consistently and correctly as described in the table below from signing of consent through 30 days from the last dose of study treatment

NOTE: Please consider use of intrauterine devices are prohibited from start of the Screening Period until EOS.

Adequate non-hormonal Contraceptive Methods

Note: Participant should use an acceptable effective method for contraception as specified in the Inclusion Criterion #8

Adequate non-hormonal Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
• Participant has undergone surgical sterilization, or • Bilateral tubal occlusion.
Vasectomized partner (at least 12 weeks before signing informed consent) *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. 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 participant.*
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.
Acceptable Birth Control Methods Which May Not be Considered as Highly Effective *Failure rate of >1% per year.*
Dual non-hormonal contraception method • Male condom combined **with** any one of the following barrier methods: o With spermicide o Diaphragm with or without spermicide o Cervical cap with or without spermicide o Vaginal sponge impregnated with spermicide **Note:** 1. Male and female condom should not be used at the same time 2. If permitted by local guidelines, contraceptive gels with other barrier methods (eg. diaphragm or cervical cap) may be used in countries where spermicides are not available.

Pregnancy Testing:

Women of childbearing potential should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.

Pregnancy testing should be performed at times specified in the SoA. Additional pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Urine pregnancy testing is to be performed using the test kit provided by the Sponsor and in accordance with instructions provided in its package insert.

Collection of Pregnancy Information

Female Participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor or designee within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor or designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor or designee as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study treatment or be withdrawn from the study. If the participant is planning to terminate the pregnancy, they can be rescreened based on the Sponsor Medical Monitor's discretion.

Appendix 6 Protocol-Specific Rescue Medication

The rescue medication will be naproxen sodium, CCI (administered per local guidelines) and will be provided by the Sponsor. The rescue medication is to be prescribed as per Investigator's discretion.

Appendix 7 Prohibited CYP3A4 Substrates, Inducers, and Inhibitors; and P-gp and BCRP Substrates

The following medications are prohibited at any time during this study.

Note: The list is intended to be a guidance and may not include all medications in the respective categories.

CYP3A4 Substrates (Sensitive)	Alfentanil, apixabane, alprazolam, aprepitant, atorvastatin, budesonide, buspirone, colchicine, conivaptan, cyclosporine, darifenacin, darunavir, dronedarone, ebastine, eletriptan, eliglustat, eplerenone, everolimus, felodipine, indinavir lomitapide, lovastatin, lurasidone, maraviroc, midazolam, naloxegol, nisoldipine, pimozide, quinidine, quetiapine, rifabutin, rilpivirine, rivaroxaban, saquinavir, simvastatin, sirolimus, tacrolimus, ticagrelor, tipranavir, tolvaptan, triazolam, and voclosporine.
CYP3A4 Inducers (Moderate and Strong)	Amprenavir, armodafinil, avasimibe, bosentan, carbamazepine, echinacea, efavirenz, etravirine, modafinil, nafcillin, nevirapine, phenobarbital, phenytoin, primidone, rifampin, and rufinamide.
CYP3A4 Inhibitors (Moderate and Strong)	Amiodarone, amlodipine, atazanavir, boceprevir, bicalutamide, chlorzoxazone, cimetidine, cilostazol, ciprofloxacin, clarithromycin, clotrimazole, cobicistat, cyclosporine, danoprevir, diltiazem, erythromycin, fluconazole, fluvoxamine, fosamprenavir, fluoxetine, ginkgo, goldenseal, grapefruit juice, isoniazid, istradefylline, itraconazole, ivacaftor, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, nicardipine, paritaprevir, posaconazole, products containing Seville oranges, ranitidine, ranolazine, rifabutin, ritonavir, telaprevir, telithromycin, tiranavir, tofisopam, troleandomycin verapamil, voriconazole, and zileuton.
Sensitive substrates for P-Gycoprotein (P-gp)	Digoxin, dabigatran etexilate, edoxaban, fexofenadine, loperamide, morphine Note: should be administered at least 4 hours apart from OG-6219
Sensitive substrates for Breast Cancer Resistance Protein (BCRP)	Rosuvastatin, sulfasalazine, methotrexate, prazosin, glyburide, teriflunomide, cladribine Note: should be administered at least 4 hours apart from OG-6219

Appendix 8 Concomitant Pain Relief Medication [redacted]

Nonsteroidal anti-inflammatory drugs (NSAID) and Others
Acetaminophen (Actamin, Altenol, Aminofen, Feverall, Genapap ,Ofirmev, Tylenol)
Aspirin (also known as acetylsalicylic acid) (Ecotrin)
Celecoxib (CeleBREX, Elyxyb)
Diclofenac (Cataflam, Cambia, Dyloject, Lofena, Pennsaid, Rexaphenac, Solaraze, Voltaren, Voltaren-XR, Zipsor, Zorvolex)
Diflunisal (Dolobid)
Etodolac (Lodine, Lodine XL)
Fenoprofen (Expron, Fenortho, Nalfon, Profeno)
Flurbiprofen (Ansaid)
Ibuprofen (Actiprofen, Addaprin, Advil, Advil Liqui-Gels, Advil Migraine, A-G Profen, Bufen, Caldolor, Genpril, Haltran, Ibu, IBU 220, Ibu-8, Ibu-6, Ibu-4, Ibu-Tab, Midol IB, Motrin, Motrin IB, NeoProfen, Nuprin, Proprinal, Q-Profen)
Indomethacin (Indocin, Indocin SR, Tivorbex)
Ketoprofen (Orudis, Orudis KT, Oruvail) / Dexketoprofen (Algoflex Neo, Keral)
Ketorolac (Sprix, Toradol)
Magnesium salicylate (Doan's Extra Strength, Doan's Regular, Keygesic-10, MST 600, Momentum, Novasal)
Meclofenamate (Meclomen)
Mefenamic acid (Ponstel,
Meloxicam (Anjeso, Mobic, Qmiiz, Vivlodex)
Nabumetone (Relafen, Refalen DS)
Nepafenac (Ilevro, Nevanac)
Naproxen (Aleve, Napronex, Flanax, mediproxen)
Oxaprozin (Daypro)
Piroxicam (Feldene)
Salsalate (Amigesic, Disalcid, Salflex, Salsitab, Mono-Gesic)
Sulindac (Clinoril)
Tolmetin (Tolectin DS, Tolectin 600)
Opioids
Hydrocodone: Vantrela, Hysingla ER, Zohydro ER
Hydromorphone: Exalgo(R), Palladone (R)
Meperidine: Demerol
Morphine: Avinza, Kadian, Arymo, MS Contin
Oxycodone: OxyContin, Roxicodone, Xtampza (TM)

Tramadol: Ultram

Combinations

Acetaminophen/aspirin, caffeine (Excedrin, Vanquish)

Acetaminophen / butalbital / caffeine / codeine (Fioricet with Codeine, Phrenilin with Caffeine and Codeine)

Acetaminophen / caffeine / dihydrocodeine (Dvorah, Panlor, Panlor DC, Panlor SS, Trezix, Zerlor)

Acetaminophen / codeine (Capital w/Codeine, Cocet , Codrix, Tylenol with Codeine, Tylenol #3)

Acetaminophen / hydrocodone (Anexsia, Co-Gesic, Hycet, Lorcet 10/650, Liquicet, Lorcet Plus, Lortab, Maxidone, Norco, Stagesic, Theracodophen Low 90, Verdrocet, Vicodin, Vicodin ES, Vicodin HP, Xodol, Zamicet, Zolvit, Zydone)

Acetaminophen / oxycodone (Endocet, Magnacet, Nalocet, Narvox, Percocet, Perloxx, Primlev, Prolate, Roxicet, Roxilox, Tylox, Xartemis XR, Xolox)

Acetaminophen/pentazocine (Talacen)

Acetaminophen/propoxyphene (Balacet, Darvocet A500, Darvocet-N 50)

Acetaminophen / tramadol (Tramapap, Ultracet)

Acetylsalicylic acid, sodium bicarbonate, and anhydrous citric acid (Alka Seltzer)

Aspirin / butalbital / caffeine / codeine (Ascomp with Codeine, Fiorinal with Codeine)

Aspirin/caffeine (Anacin, Bayer Aspirin, BC Arthritis, Goody's)

Aspirin / caffeine / dihydrocodeine (Synalgos-DC)

Aspirin / oxycodone (Endodan, Percodan)

Belladonna / opium (B&O Supprettes)

Buprenorphine / naloxone (Bunavail, Cassipa, Suboxone, Zubsolv)

Celecoxib / tramadol (Seglentis)

Diclofenac / misoprostol (Arthrotec)

Esomeprazole / naproxen (Vimovo)

Famotidine / ibuprofen (Duexis)

Hydrocodone / ibuprofen (Ibudone, Reprexain, Vicoprofen)

Ibuprofen/Caffeine (Algoflex duo)

Ibuprofen / oxycodone (Combunox)

Metamizole/ caffeine / drotaverin-hydrochloride (Quarelin)

Morphine / naltrexone (Embeda)

lansoprazole/naproxen (Prevacid NapraPAC)

Naloxone / pentazocine (Talwin Nx)

Naloxone / oxycodone (Targiniq ER)

Naltrexone / oxycodone (Troxyca ER)

Appendix 9 Country-specific Requirements

9.1 Specific requirements for France

Requirements for Section 8.1.5

Race will not be collected for participants in France (see section 8.1.5) as the collection and processing of personal data that reveals, directly or indirectly, the racial and ethnic origins, the political, philosophical, religious opinions or trade union affiliation of persons, or which concerns their health or sexual life, is prohibited. This is based on France's Data Protection Act No. 78-17 created the French Data Protection Authority (Commission Nationale Informatique et Libertés [CNIL]) (see 8.1.5).

Appendix 10 Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC).

Amendment 01 (16-Sep-22)

Overall Rationale for the Amendment:

Initial findings from non-clinical study have indicated that concomitant medications that are sensitive substrates of P-glycoprotein (P-gp) or Breast Cancer Resistance Protein (BCRP) should be administered 4 hours apart from OG-6219 intake. Therefore, the protocol OG6219-P001 has been amended to add this non-clinical information, address United States Food and Drug Administration (FDA) comments and to improve the readability.

Section number and Change	Description of Change (the information added is shown in quotes, and deleted information is shown as a strike-out)	Brief Rationale
Title page Synopsis	• Protocol number updated to OG6219-P001-02 • EU CTR number added	To update administrative information.
Synopsis/ Rationale Section 4.2 (Scientific Rationale for Study Design) Throughout the document	• The overall pelvic pain (OPP) denotes "endometriosis-related" overall pelvic pain, • The non-menstrual pelvic pain score (NMPP) includes "pain associated with micturition, defecation, ovulation, intercourse"	To provide clarity on pelvic pain (OPP and NMPP) definitions and their relationship only with endometriosis.
Synopsis/ Secondary Objectives and Endpoints Section 3 (Objectives and Endpoints)	• For secondary objective #6, the corresponding endpoint sampling time for PK parameters C_{max}, T_{max}, and AUC_{tau} was clarified to be CCI [redacted]	To provide clarity on when PK assessment is to be performed.
Synopsis/ Secondary Objectives and Endpoints Section 3 (Objectives and Endpoints)	• For the secondary objective #12 endpoint of mean change from BC to TRC3 "of the monthly dyspareunia score" was added	To provide clarity that from BC to TRC3 relates to the monthly dyspareunia score.
Synopsis/Statistical Methods Section 9.5 (Interim Analysis)	• IA was added to the synopsis • Interim psychometric evaluation of blinded data was added during IA	To include psychometric analysis of blinded data in the IA.
Section 1.3 (Schedule of Activities)	• In footnote e: clarified that the PAP smear should be performed "at Screening"	To provide clarity on when PAP smears are to be performed.

Section number and Change	Description of Change (the information added is shown in quotes, and deleted information is shown as a strike-out)	Brief Rationale
Section 1.3 (Schedule of Activities) CCI	• CCI • Additional changes were made to the section title and CCI to be entered in the eCRF	To provide clarity on CCI
Section 2.3.1 (Risk Assessment) Section 2.3.3 (Overall Benefit Risk Conclusion) Section 5.3 (Lifestyle Considerations) Appendix 5 (Contraceptive and Barrier Guidance and Collection of Pregnancy Information)	• Clarified acceptable contraceptive use • Added that participants who are willing to reliably use "an acceptable effective method for contraception" may be eligible. The acceptable methods include effective methods of contraception (references to double barriers and highly effective contraception were removed)	To clarify acceptable methods for contraception, use and correct the contraceptive terminology related to effective versus highly effective methods based on CTFG guidance [65]
Section 2.3.1 (Risk Assessment) Section 2.3.3 (Overall Benefit Risk Conclusion) Section 6.8.2 (Prohibited Medications and Other Products) Appendix 7	• Added "OG-6219 and FOR-1011 were found to inhibit P-glycoprotein (P-gp) and/or Breast Cancer Resistance Protein (BCRP) transporters in vitro, thus concomitant administration of OG-6219 with sensitive P-gp and BCRP substrates should be avoided." • Concomitant medications that are sensitive substrates of P-gp or BCRP should be administered at least 4 hours apart from administration of OG-6219. • The lists of medications that are sensitive substrates for P-gp and BCRP were added to Appendix 7.	To specify how medications that are sensitive substrates of P-gp or BCRP should be administered in relation to OG-6219 intake to avoid possible DDIs with regard to these transporters.
Section 1.3 (SOA) – footnote y Section 2.3.1 (Risk Assessment) Section 2.3.3 (Overall Benefit Risk Conclusion) Section 7.2 (Participant Discontinuation/Withdrawal from the Study Section 8.3.4 (Columbia-Suicide Severity Rating Scale (C-SSRS)	• Added "Based on determination of positive C-SSRS results for suicidality and its severity, the participants will be discontinued from the study medication and referred to a specialist at the Investigator's discretion for further evaluation. In addition, the positive results from C-SSRS evaluation will have to be treated as an SAE and reported to the Sponsor in a timely manner." • Added the study discontinuation criterion for "participants who experience suicidal ideation or attempt suicide" • Added the following sentence: "Suicidality will be monitored throughout the study employing a validated questionnaire C-SSRS."	To provide steps taken with a positive C-SSRS result.

Section number and Change	Description of Change (the information added is shown in quotes, and deleted information is shown as a strike-out)	Brief Rationale
Section 5.1 (Inclusion Criteria) Table 2: Prohibited Medication and Other Substances Section 8.2.2.4 Prohibited Pain Medication Use	• Clarified that CCI [redacted] (ie, CCI [redacted] of ~~other NSAID or non-opioid~~ pain medications for acute conditions other than ERP is permitted	For clarification CCI [redacted] of pain medication in Inclusion Criterion #13 and other sections in the protocol as listed.
Section 5.2 (Exclusion Criteria)	CCI [redacted]	For clarification.
Section 5.2 (Exclusion Criteria)	• Corrected EC#3 to include "clinically" as follows: Has a "clinically" significant gynecologic condition • Revised exclusion criteria #14 as follows: Has a known human immunodeficiency virus infection, "and/or" active, recurrent, or chronic infection (eg, hepatitis A, B, or C virus)	For clarification.
Section 6.6 (Continued Access to Study Treatment after the End of the Study)	• Changed as follows: The Sponsor will not provide additional care to the participants after they ~~leave~~ "complete or discontinue" the study.	To use consistent terminology.
Section 6.9 (Study Treatment Accountability)	• Corrected that the quantity of dispensed study treatment will be recorded on study treatment accountability forms and entered in the "IRT". • Corrected that the use of rescue medication will also be recorded in the IRT "and eDiary"	To correct of documentation methods used.
CCI [redacted]		To correct the error.
Section 8.3.2 (Vital Signs)	• Deleted specific instructions related to blood pressure	Standard procedure.
Section 8.4.1 (Time Period and Frequency for Collecting AE and SAE Information) – Table 7	• Revised that for Overdose, report if receiving CCI [redacted] or other CCI [redacted] medication "(including Rescue Medication)" • Added, "For SAEs, standard procedures for reporting (within 24 hours) must be followed"	To clarify the use of Rescue Medication and to specify that for SAE the standard procedures for reporting (within 24 hours) must be followed.

Section number and Change	Description of Change (the information added is shown in quotes, and deleted information is shown as a strike-out)	Brief Rationale
Appendix 2 (Regulatory, Ethical, and Study Oversight Considerations)	• For Quality Assurance, added that the "eDiary" data will be transmitted to the Sponsor or designee electronically.	For clarification.
Appendix 3 (Clinical Laboratory Tests)	• In Table 9 (Protocol-required Safety Laboratory Tests) the following coagulation tests were added: prothrombin time, activated partial thromboplastin time, and antithrombin III • Revised Urinalysis as follows: Microscopy ~~(if clinically indicated)~~	Added evaluations for coagulation as recommended by the FDA, and indicated that Microscopic evaluation for Urinalysis will be for all participants.
Appendix 7	• Added, "Note: The list is intended to be a guidance and may not include all medications in the respective categories"	Added guidance.
Appendix 9 (Protocol Amendment History)	• Section added	Section to be added for amendments.
Throughout the document	• Minor editorial updates	For better readability.

Amendment 02 (03-Jan-2023)

Overall Rationale for the Amendment:

The protocol OG6219-P001-01 was amended to address European Medicines Agency (EMA) feedbacks.

Section number and Change	Description of Change (the information added is shown in bold, and deleted information is shown as a strike-out)	Brief Rationale
Section 1.3 Serum Pregnancy Test (β-hCG)	• Serum Pregnancy Test was added to CCI [redacted]	Agreement with EMA suggestion
Section 1.3 Footnote g	The footnote g was changed to: The UPT is centrally provided. If any menstrual cycle delay is noted, the participant must immediately perform UPT and contact clinic to schedule a visit as soon as possible and the Sponsor must be contacted. Additional UPT can be dispensed as needed.	Clarify that when a menstrual delay is noted, the participant must immediately perform UPT and contact the clinic.
Introduction	• The introduction was modified as follows: • ~~The HSD17β1 in primates, is primarily expressed in the placenta and ovary and to a lesser extent in the endometrium, adipose tissue, and prostate. The HSD17β~~	Include recent published information

Section number and Change	Description of Change (the information added is shown in bold, and deleted information is shown as a strike-out)	Brief Rationale
	~~expression in the human endometrium is not detected until Day 14 of the menstrual cycle~~ HSD17β1 expression is seen in the eutopic endometrium throughout the cycle. The HSD17β1 and HSD17β2 are both expressed in endometrium and endometriotic implants; however, there is an imbalance between HSD17β1 and β2 in endometriotic lesions as compared to normal endometrium (eutopic endometrium). • **In a recently published study, in which protein levels of different enzymes were determined in both eutopic endometrium and endometriotic lesions, eutopic endometrium presented higher levels of aromatase, compared to steroid sulfatase (STS) or HSD17β1, while endometriotic lesions had superior levels of STS and HSD17β1.**	
2.3.1 Risk assessment	• Modified the following: • Any **potentially deleterious** effect on the endometrium will be monitored by TVUS or transabdominal (pelvic) ultrasound and endometrial biopsies during Screening up to TRC3 CCI [redacted]	Clarification
2.3.1 Risk assessment	• Modified the following: • However, **as** the effect of OG-6219 on fertility and early embryonic development and pre-and post-natal development has not been studied at this time, **the risk of reproductive toxicity cannot be considered fully characterized**.	Clarification
2.3.3 Overall Benefit Risk Conclusion	• Clarified that the lower doses of CCI [redacted] BID are planned based on Phase 1 PK modeling data	Agreement with EMA suggestion
4.3 Justification for dose	• Modified the following: • **In this Phase 2a/b study, the lower doses of** CCI [redacted] **BID planned-are based on Phase 1 PK modeling data.** • ~~In this Phase 2a/b study, all the lowest dose of~~ CCI [redacted] ~~BID planned is expected to be less effective or have no effect, assuming dose linearity and observed plasma PK.~~	All three dose levels chosen (CCI [redacted] BID) are anticipated to be efficacious based on Phase 1 PK modeling data (therefore 'no effect' is incorrect).

Section number and Change	Description of Change (the information added is shown in bold, and deleted information is shown as a strike-out)	Brief Rationale
5.1 Inclusion Criteria Inclusion criterion 04 (IC04)	• IC04 was modified as follows: • Has had spontaneous (ie, without hormonal therapy), regular, menstrual cycles with a cycle length between 21 to 32 days (inclusive) for the past ~~2~~ 1 months before V1. **Note: Peri-menopausal women have irregular menstrual cycles, and don't meet this inclusion criterion, and should not be included**.	Clarify the peri-menopausal participants are excluded
5.2 Exclusion Criteria Exclusion criterion 7 (EC7)	• EC7 was modified as follows: • Has no documented normal Papanicolaou (PAP) test within the timeline of current standard of care guidelines or has a significantly abnormal PAP test at Screening (V1) (ie, ~~atypical squamous cells~~, low grade squamous intraepithelial lesion, high grade squamous intraepithelial lesion, atypical glandular cells [any type], squamous cell carcinoma, or adenocarcinoma [in situ or invasive]). The presence of high-risk human papillomavirus (HPV), regardless of PAP result, is exclusionary **(e.g. atypical squamous cells)**.	Clarification
5.2 Exclusion Criteria Exclusion criterion 14 (EC14)	• EC14 was modified as follows: • Has a known human immunodeficiency virus infection, and/or an **acute** or active, recurrent/**relapsing**, or chronic infection (eg, hepatitis A, B, or C virus).	Clarification
5.2 Exclusion Criteria Exclusion criterion 22 (EC22)	• EC22 was modified as follows: • Based on the known metabolism of OG-6219 there are no effects of alcohol, caffeine, or tobacco associated with study treatment. However, during the study participants are asked to refrain from • Excessive tobacco use and smoking CCI [redacted] CCI [redacted] based on Investigator's discretion.	Clarified CCI [redacted] is an exclusion criterion
5.2 Exclusion Criteria Table 2	• Table heading changed to: Prohibited Medication, Contraceptive Devices and Other Substances • Also Modified the text in the table as follows: • The following medications, **contraceptive devices and other substances** are prohibited at any time	Clarify that Contraceptive Devices are also listed in the table as being prohibited

Section number and Change	Description of Change (the information added is shown in bold, and deleted information is shown as a strike-out)	Brief Rationale
	during the participant's participation in this study	
	• Section subheading changed to: Prohibited Medications: Hormones and Contraceptive Devices	Clarify that Contraceptive Devices are listed in the table as being prohibited
	• Included Hormonal Replacement Therapy (HRT)	Specify that HRT is a prohibited medication
	• Changed the description for CCI [redacted] • [redacted] • Footnote b was modified as follows: • Participants with an ~~No intrauterine device~~ IUD (non-hormonal) ~~must be removed before~~ **on the day of the** Screening Visit **are excluded.**	Clarify that any CCI [redacted] taken for chronic pain is prohibited
5.3 Lifestyle consideration	• The following changes were made: • Excessive tobacco uses and smoking has been restricted based on Investigator's discretion. Abuse of alcohol is prohibited. Alcohol intake should be limited to 2 to 3 units per day, not to exceed 14 units per week. **Active use of illicit drugs** CCI [redacted] **is prohibited.** • Note: CCI [redacted] (prescribed) for chronic pain use is prohibited. Refer to Table 2 for a list of prohibited medications.	Clarification on use of CCI [redacted]
8.1.5 Demography	• Specific requirements were added for France	Specify requirements for France on collection of demography data
8.3.6 Endometrial Biopsy	• The following changes were made: • **If the results of an endometrial biopsy are abnormal the participant will be informed of the results and appropriate clinical follow-up is required. If abnormal results are at Screening, the participant will be screen failed**. • ~~If the results of an endometrial biopsy are abnormal the participant will be informed of the results and advised as to any medically appropriate follow-up~~.	Clarification on endometrial biopsy results

Section number and Change	Description of Change (the information added is shown in bold, and deleted information is shown as a strike-out)	Brief Rationale
8.4.4 Regulatory Reporting Requirements	• The following was added: • **SUSAR reports will be submitted electronically (gateway to gateway) from the sponsor's safety database to the EudraVigilance Clinical Trial Module, in accordance with the EU Clinical Trial Regulation.**	Added procedure for reporting of SUSARs by the sponsor
Appendix 2	• Recruitment information was added and the heading was changed to **Recruitment and Informed Consent** • Subheading styles were changed • For Data Protection, the following was added: The contract between sponsor and study sites and any applicable third part involved in the trial specifies responsibilities of the parties related **to** data protection, , including handling of data security breaches and respective communication and cooperation of the parties.	Include recruitment procedures. Subheading styles were changed for easier viewing and navigation.
Appendix 5	• The following was added: **Dual non-hormonal contraception method** • Male condom combined with any one of the following barrier methods: ○ With spermicide ○ Diaphragm with or without spermicide ○ Cervical cap with or without spermicide ○ Vaginal sponge impregnated with spermicide **Note:** 1. Male and female condom should not be used at the same time 2. If permitted by local guidelines, contraceptive gels with other barrier methods (eg. diaphragm or cervical cap) may be used in countries where spermicides are not available.	Clarify contraceptive requirements.
Appendix 8	• This is a new appendix that was added: **Concomitant Pain Relief Medication** CCI [redacted]	Clarify pain medications allowed CCI [redacted]

Section number and Change	Description of Change (the information added is shown in bold, and deleted information is shown as a strike-out)	Brief Rationale
Appendix 9	• Specific requirements for France were added as race will not be collected	EMA feedback based on France's Data Protection Act No. 78-17 created the French Data Protection Authority (Commission Nationale Informatique et Libertés [CNIL])
Appendix 10	• Protocol Amendment History was added	Template specification
Appendix 11: Data Protection	• The following was added • **The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.** • **Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.**	Clarify data protection procedures
Throughout the protocol	• Minor edits and corrections	Clarity

Amendment 03 (10-Feb-2023)

Overall Rationale for the Amendment:

The protocol OG6219-P001-01 has been amended to address Food and Drug Administration (FDA) questions.

Section number and Change	Description of Change (the information added is shown in bold, and deleted information is shown as a strike-out)	Brief Rationale
Section 1.1 Synopsis and Section 3 Objectives and Endpoints (Table 1)	• The Objective and Endpoint Table have been reorganized into Secondary Efficacy, Safety, and PK/PD Endpoints with further editorial revisions made to the content • Text has been added that the primary efficacy, primary safety, and secondary efficacy endpoints will be assessed comparing Group A (CCI BID), B (CC	Clarification of endpoints

Section number and Change	Description of Change (the information added is shown in bold, and deleted information is shown as a strike-out)	Brief Rationale
	C BID), C (CCI BID) with Group D (Placebo) • Footnote [a] was added to define OPP as the combination of the DYS and NMPP scores	
Section 1.1 Synopsis	Modify text in Rationale: The primary efficacy endpoint will assess the efficacy of 3 dose levels of OG-6219 in change from Baseline Cycle (BC) in endometriosis-related overall pelvic pain (OPP) score (the **weighted** mean of the dysmenorrhea [DYS] pelvic pain score ~~combined with the mean of~~ and the non-menstrual pelvic pain score [NMPP; pain associated with micturition, defecation, ovulation, intercourse]) during the Treatment Cycle 3 (TRC3) compared to Placebo.	Clarify the primary endpoint
Section 1.1 Synopsis and Section 9.4.2 Primary Endpoint Analysis	Added sentence to include alternate error structures: **If nonconvergence is encountered, compound symmetry (CS) and first-order autoregressive AR(1) error structures will be considered.**	Agreement with FDA
Section 1.1 Synopsis and Section 9.4.3 Secondary Endpoint Analysis	Added sentence to include alternate error structures: **If nonconvergence is encountered, CS and AR(1) error structures will be considered**	Agreement with FDA
Section 1.3 Schedule of Activities (footnote y), 2.3.1 Risk Assessment, Section 2.3.3 Overall Benefit Risks Conclusion, Section 8.3.4 Columbia Suicide Severity Rating Scale (C-SSRS)	Deleted text: Based on determination of positive C-SSRS results for suicidality ~~and its severity~~, the participants will be discontinued from the study medication and referred to a specialist at the Investigator's discretion for further evaluation.	Clarification that Study is not evaluating the severity
Section 2.3.1 Risk Assessment and Section 7.3 Criteria for Study Termination	Clarification on • DMC role • independent safety monitoring and study stopping criteria to align with DMC charter	Agreement with FDA
Section 5.2 Exclusion Criteria	Exclusion criteria #9 has been modified: Has a history of malignancy ≤5 years before signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. **Note: Any history of hormonal sensitive malignancy (eg, breast**	Agreement with FDA

Section number and Change	Description of Change (the information added is shown in bold, and deleted information is shown as a strike-out)	Brief Rationale
	or ovarian cancers) excludes the participant.	
Section 6.7 Treatment Overdose	Clarified text on time frame to report an overdose	Agreement with FDA
Section 7.2 Participant Discontinuation/Withdrawal from the Study	Updated bullet on ECG: • ECG findings of QTcF prolongation of ~~500~~ CCI [redacted], or a change of >60 ms from the pre-dose ECG, based on the average of triplicate ECGs Added new bullets • **Safety recommendation based on DMC / investigator/ Sponsor assessment of AEs and AESI** • **If the participant undergoes urgent surgical procedures for endometriosis-related pain**.	Agreement with FDA / clarification
Section 8.3.4 Columbia Suicide Severity Rating Scale (C-SSRS)	Added text to provide a threshold score using the Columbia Suicide Severity Rating Scale (C-SSRS) that subjects must reach for the investigator to discontinue the subject from clinical trial.	Agreement with FDA
Section 8.4.1 Time Period and Frequency for Collecting AE and SAE Information	Modified Table 7 Overdose row to clarify text on time frame to report an overdose.	Clarification and align with Section 6.7 Treatment Overdose
CCI [redacted]	• [redacted] • [redacted]	[redacted]
[redacted]	Modified text CCI [redacted]	Clarification
Section 9.4.7.1 Adverse Events	Added text: **The timeframe for a TEAE after stopping the randomized treatment is 14 days.**	Clarification
Throughout the protocol	• Minor edits and corrections	Clarity

Amendment 04 (16-Jun-2023)

Overall Rationale for the Amendment:

The protocol OG6219-P001-03 has been amended to address Food and Drug Administration (FDA) questions and make clarifications to the protocol.

Section number and Change	Description of Change (the information added is shown in bold, and deleted information is shown as a strike-out)	Brief Rationale
Section 1.1 Synopsis (Overall Design), Section 3.0 Objectives and Endpoints (footnote to Table 1), Section 4.1 Overall Design, Appendix 1 Definitions	Modified text ○ TRC2 is the period between the first day of second menses after ~~TRC1~~ **end of BC** to the day prior to first day of next menses, regardless of number of days. Phone Contact C is done during the menses. TRC3 or EOT is the period between the first day of third menses after ~~TRC2~~ **end of BC** to either end after C completed cycles or CCI on study treatment, whichever occurs first.	Clarification
1.3 Schedule of Activities	Modified Footnote h C : Participant must be CCI compliant with CCI to be randomized~~. (information to be provided by the eDiary portal).~~	Clarification
	Modified Footnote l During the ~~site~~ **study** visit, the PRO should be completed prior to other types of study procedures, such as blood draws and physical examinations.	Clarification
	Modified Footnote v C sample collection ~~should~~ **to be collected** within 12±4 hours of last dose of study medication. **If not possible, the PK sample should be collected at C irrespective of the timing of the last study dose taken.**	Clarification that C PK sample must be taken even if not possible within stated window of time.
5.2 Exclusion Criteria	Modified Exclusion Criterion #9. Has a history of malignancy ≤5 years before signing informed consent except for adequately treated basal cell or squamous cell skin cancer ~~or in situ cervical cancer.~~	Agreement with FDA
	Modified Exclusion Criterion #22 to exclude the use of CCI (per cycle). Based on the known metabolism of OG-6219 there are no effects of alcohol, caffeine, or tobacco associated with study treatment. However, during the study participants are asked to refrain from:	Response to FDA/ clarify use of CCI compounds

Section number and Change	Description of Change (the information added is shown in bold, and deleted information is shown as a strike-out)	Brief Rationale
	a) Excessive tobacco use and smoking (including ~~excessive recreational marijuana~~ CCI based on Investigator's discretion. CCI **(ie,** CCI CCI	
5.2 Exclusion Criteria Table 2 Prohibited Medication, Contraceptive Devices and Other Substances	Table 2. Prohibited Medications: Analgesics Deleted text on CCI CCI ~~Any prescribed~~ CCI ~~for chronic pain management~~	Clarification to Table 2 for category of Other Prohibited Medications. Response to FDA/ clarify use of CCI compounds
	Prohibited Medications: Other Added CCI CCI **compounds are permitted.**	Response to FDA/ clarify use of CCI compounds. Added cannabis to "other"
5.3 Lifestyle considerations	Modified Note: ~~Non-excessive~~ CCI CCI CCI **compounds are permitted (usage must be recorded).** CCI ~~(prescribed) for chronic pain use is prohibited.~~ Refer to Table 2 for a list of prohibited medications.	Response to FDA/ clarify use of CCI compounds
Section 6.1 Study Treatments Administered	Modified Table 6. Non-Investigational Medicinal Products / Rescue Medication Packaging and Labeling: ~~For US the product will be provided in commercial bottles. For EU the product will be provided in commercial blister packs.~~ ~~All packs will be labeled as required per country requirements.~~ **Product will be provided in commercial packaging and will be labeled as required per country requirements.** Sourcing: Provided centrally by the Sponsor. In special circumstances, may be	Clarification to country-specific text to make protocol global. Deleted manufacturer as source may change depending on region/country

Section number and Change	Description of Change (the information added is shown in bold, and deleted information is shown as a strike-out)	Brief Rationale
	provided locally with prior approval from the Sponsor. ~~Manufacturer (Central Supply):~~ ~~US: Glenmark Pharmaceuticals~~ ~~EU: KRKA, dd~~	
Section 8.5.1 Collection of Samples	Table 8. Schedule of Pharmacokinetic samples Modified footnote c C sample collection ~~should~~ **to be collected** within 12±4 hours of last dose of study medication. **If not possible, the PK sample should be collected at** C **irrespective of the timing of the last study dose taken.**	
Appendix 4	Modified Events Meeting the AE Definition Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment 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 s should be reported regardless of sequelae.~~ **All overdose events must be reported in accordance with its seriousness including overdose taken with intentional suicidal/self-harming intent**.	Clarification

Amendment 05 (07-Nov-2023)

Overall Rationale for the Amendment:

The protocol OG6219-P001-05 has been amended to address a Food and Drug Administration (FDA) question and make clarifications to the protocol.

Section number and Change	**Description of Change (the information added is shown in bold, and deleted information is shown as a strike-out)**	**Brief Rationale**
Study Schema	Change Screening period: ~~Up to~~ ~ 8 weeks Change Run-in period ~ 4 weeks Modified period between Visit 1 and Visit 2: ~~Up to~~ ~ 4 weeks Added to list of abbreviations: ~ = **approximately**	Clarification
Table 1.3 Schedule of Activities	Changed Screening on line 1 ~~Up to~~ ~12 weeks Added to list of abbreviations: ~ = **approximately**	Clarification
Section 5.2 Exclusion criterium #9	Has ~~a~~ **no** history of malignancy ~~≤5 years before signing informed consent~~ (except ~~for adequately treated~~ basal cell or squamous cell skin cancer**) before signing informed consent**.	Agreement with FDA
Table 8. Schedule of Pharmacokinetic Sampling	Footnote a Morning dose is ~~specified~~ **preferred** for pre-witness dose.	Clarification
Section 2.2 and 10 References	Corrected cross-reference and updated reference list	Incorrect citation

Appendix 11 Signature of Investigator

PROTOCOL TITLE: A Phase 2a/b, Randomized, Double-blind, Placebo-controlled, Parallel group, Multicenter, Clinical Study to Evaluate the Efficacy and Safety of OG-6219 in 3 Dose Levels, in Women 18 to 49 Years of Age with Moderate to Severe Endometriosis-related Pain

PROTOCOL NO: OG-6219-P001

VERSION: Amendment 06

This protocol is a confidential communication of Organon LLC. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study site in which the study will be conducted. Return the signed copy to Organon LLC.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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DOCUMENT ID: 0FHHT0

FILE NAME: 001-06

ELECTRONIC SIGNATURES	
Signed By:	**Meaning of Signature** **Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)**
PPD	Management Approval 16-Feb-2024 15:42:32 GMT+0000