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Official Title:	A randomized, double-blind, open for active comparator, parallel-group, multicenter Phase 2b study to assess the efficacy and safety of three different doses of P2X3 antagonist (BAY 1817080) versus placebo and elagolix 150 mg in women with symptomatic endometriosis
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Title Page

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Protocol Number: 20584

Protocol Version: 3.0

Amendment Number: 2

Compound Number: BAY 1817080

Brief Title: Assess efficacy and safety of three different doses of P2X3 antagonist in women with symptomatic endometriosis

Study Phase: **2b**

Acronym: SCHUMANN

Sponsor Name: Non-US territory: Bayer AG, US territory: Bayer HealthCare Pharmaceuticals Inc.

Legal Registered Address:

Non-US: Bayer AG, 51368 Leverkusen, Germany

US territory: Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA

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Amendment Date: **27JAN 2022**

Medical Monitor name and contact information will be provided separately.

Name: PPD PPD Role: PPD

This is an electronically generated document that does not bear any sponsor signatures. The signature of the sponsor's medically responsible person is filed in the TMF and available on request.

Document History Table

DOCUMENT HISTORY		
Document	**Version**	**Date**
Amendment 2	3.0	27 JAN 2022
Amendment 1	2.0	22 JUN 2021
Local Amendment CHN-1	Not applicable	11 JAN 2021
Original Protocol	1.0	25 SEP 2020

Protocol Amendment Summary of Changes Table

Amendment 2 (27 JAN 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Bayer has decided for a clinical hold with an immediate stop of treatment of this Phase 2b study with BAY 1817080.
Considering one confirmed and one potential case of drug-induced liver injury (DILI) in patients exposed to BAY 1817080 for 812 weeks of treatment during the phase 2 program in all indications, the benefit-risk ratio for the ongoing study 20584 is no longer considered to be positive.

No new patients should be enrolled into the study and no study participants should be randomized.
Study participants who are currently treated should immediately stop treatment and participants who have been randomized should not start treatment with the study drug, respectively. Study participants randomized to the open label elagolix arm can continue taking tablets from the current blister but must not start with a new one.
All participants should come to the end of treatment and follow up visits as soon as possible.

Following are the description of change and a brief rationale.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA) Section 1.2 Schema Section 4.1 Overall Design	Visits 5a and 6a were added for additional safety laboratory tests. All participants, except those randomized to elagolix, will have a 90-day follow up	Comprehensive safety follow up of study participants exposed to BAY1817080
Section 2.3.1 Risk Assessment	Text on potential changes in liver function laboratory parameters updated	Updated benefit/risk assessment
Section 2.3.3 Overall Benefit-Risk Conclusion	Text updated to reflect the updated benefit/risk assessment	Updated benefit/risk assessment
Section 8.3.7 Adverse Events of Special Interest Section 10.6.2 Close observation of participants with ALT or AST > 3 x ULN	Abnormal laboratory results meeting the criteria of transaminases (ALT and/or AST) >8x ULN or >3x ULN with total bilirubin >2x ULN will be reported as adverse	Comprehensive safety follow up of exposed study participants

	events of special interest.	
Section 10.2 Appendix 2 Clinical Laboratory tests	Measurement of total bile acids was added to the biochemistry laboratory parameters.	Comprehensive safety follow up of exposed study participants
Section 10.6.2 Close observation of participants with ALT or AST > 3 x ULN	Liver imaging was added to the close observation assessments, and HCV-RNA was added to the parameters for samples to be analyzed for initial close liver observation.	Comprehensive safety follow up of exposed study participants

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A randomized, double-blind, open for active comparator, parallel-group, multicenter Phase 2b study to assess the efficacy and safety of three different doses of P2X3 antagonist (BAY 1817080) versus placebo and elagolix 150 mg in women with symptomatic endometriosis

Brief Title: Assess efficacy and safety of three different doses of P2X3 antagonist in women with symptomatic endometriosis

Rationale: This study is designed to investigate effects of three different doses of BAY 1817080, i.e., 150 mg, 75 mg and 25 mg, twice daily on endometriosis-associated pelvic pain over a 12-week intervention period in comparison to placebo and elagolix 150 mg once daily.

Objectives and Endpoints and/or estimands:

Objectives	Endpoints
Primary	
• To assess the dose-response relationship and demonstrate efficacy of BAY 1817080 compared to placebo in women with symptomatic endometriosis	• Absolute change in mean worst EAPP from baseline to end of intervention (measured daily on the NRS by item 1 of the ESD)
Secondary	
• To identify at least 1 superior effective dose of BAY 1817080 compared to placebo • To evaluate the safety and tolerability of 3 doses of BAY 1817080 compared to placebo and elagolix 150mg in women with symptomatic endometriosis	• Absolute change in mean worst EAPP from baseline to end of intervention (measured daily on the NRS by item 1 of the ESD) • Number of participants with treatment emergent adverse events

Overall Design:

This is a parallel-group intervention study in endometriosis patients with 5 treatment groups, including a double-blinded placebo treatment group and an open-label active comparator treatment group.

Participants who fulfill all eligibility criteria will be randomized to receive:

- BAY 1817080 (150 mg, 75 mg, or 25 mg BID) OR
- elagolix (150 mg QD), OR
- placebo

Brief Summary:

The purpose of this study is to assess safety and efficacy of BAY 1817080 compared to elagolix and placebo in women with symptomatic endometriosis. Study details include:

- Study duration: 155 up to 285 days
- Treatment duration: 84 days

- Visit frequency: approximately once a month

Study interventions will not be available through an expanded access program.

Number of Participants:

Approximately 840 participants will be screened to start study intervention in about 420 randomized participants for at least 50 participants evaluable for the primary analysis (i. e. included in the pPPS) per intervention group.

Intervention Groups and Duration:

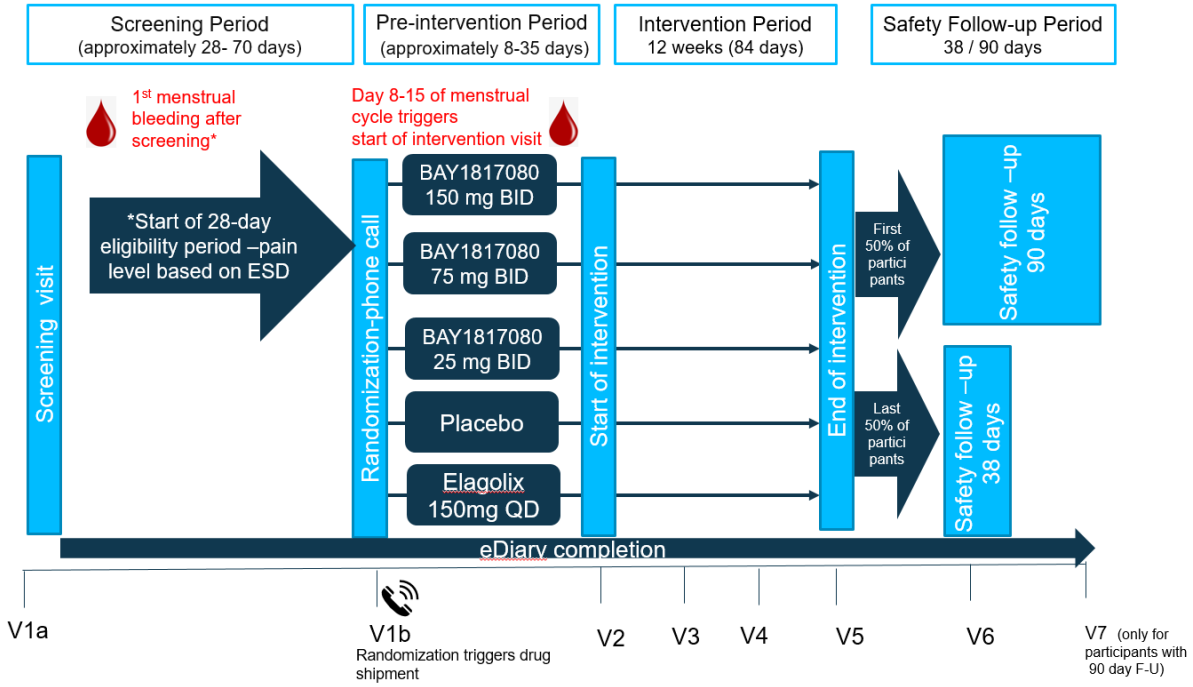
Study Periods	**Duration**
1. Screening 2. pre-intervention 3. Intervention 4. Follow-up	1. 28 to 70 days (4 to 10 weeks) 2. approximately 8-35 days 3. 84 days (12 weeks) 4. 38 or 90 days (5-13 weeks)
Total number of participants	**Total study duration**
420 treated	155 to 285 days

Intervention groups:

- Group 1: 150 mg of BAY 1817080 BID
- Group 2: 75 mg of BAY 1817080 BID
- Group 3: 25 mg of BAY 1817080 BID
- Group 4: placebo
- Group 5: elagolix 150 mg QD

Data Monitoring Committee: no

1.2 Schema



*Follow-up 2 will be performed in all randomized participants, except for those randomized to the open label elagolix arm. Follow-up 2 will extend to 90±3 days after the last administration of study intervention
In addition to visits displayed in the schema, 5 additional visits (2a, 3a, 4a, 5a and 6a) are included for taking blood samples for liver monitoring, see SoA for details.

1.3 Schedule of Activities (SoA)

Procedure	Screening Period	Pre-Intervention Period[1]	Intervention Period (Days)							Follow-up Period				Notes
	28 to 70 days	8 to 35 days	1	14 ±3	28 ±3	42 ±3	56 ±3	70 ±3	84 +3	14 ±3 days after the last dose	38 ±3 days after the last dose	68 ±3 days after the last dose	90 ±3 days after the last dose	
Visit number	1a[2]	☎ (1b)	2	2a	3	3a	4	4a	5	5a	6	6a	7	Visit 5 is to be performed as the end of intervention visit in case of a premature discontinuation
Informed consents														
Informed consent	X													
Informed consent for genetic sampling (optional)	X													Can be done at either Visit 1a or 2
Informed consent for actigraphy (optional)	X													
Baseline characteristics and medical history														
Demography	X													
Eye and hair color	X													Natural hair color at age 18 Collection of eye and hair color as recommended by the World Endometriosis Research Foundation Endometriosis Phenome and biobanking harmonization project (1)

[1] At day 28 of the menstrual cycle starting at or after Visit 1a at least 24 available entries in the ESD item 1 ('worst pain' on the daily numerical rating scale; 24-hour recall) sum up to 98 or more.

[2] Ultrasound and cervical smear sampling can be done on a different day from other screening procedures.

Procedure	Screening Period	Pre-Intervention Period[1]	Intervention Period (Days)							Follow-up Period				Notes
	28 to 70 days	8 to 35 days	1	14 ±3	28 ±3	42 ±3	56 ±3	70 ±3	84 +3	14 ±3 days after the last dose	38 ±3 days after the last dose	68 ±3 days after the last dose	90 ±3 days after the last dose	
Visit number	1a[2]	☎ (1b)	2	2a	3	3a	4	4a	5	5a	6	6a	7	Visit 5 is to be performed as the end of intervention visit in case of a premature discontinuation
History of endometriosis surgery	X													
Previous medical treatments relevant for endometriosis	X													
Reproduction and menstrual history	X													
Medical history and concurrent medical conditions	X													Medical occurrences that began before the signing the informed consent form Endometriosis or chronic pelvic pain diagnosed in female blood relatives
Diagnosis of endometriosis and confirmation of moderate to severe pelvic pain														
Confirmation of previous endometriosis diagnosis	X													Ultrasound confirmation, if needed (for Japanese participants only) (Section 5.1: Inclusion criterion #1 in the category „Type of participant and disease characteristics“)
ESD eligibility check		X												Check eligibility as per Inclusion criteria #3 from eDiary for a) compliance with daily entries and b) average of pain scores

Procedure	Screening Period	Pre-Intervention Period[1]	Intervention Period (Days)							Follow-up Period				Notes
	28 to 70 days	8 to 35 days	1	14 ±3	28 ±3	42 ±3	56 ±3	70 ±3	84 +3	14 ±3 days after the last dose	38 ±3 days after the last dose	68 ±3 days after the last dose	90 ±3 days after the last dose	
Visit number	1a[2]	☎ (1b)	2	2a	3	3a	4	4a	5	5a	6	6a	7	Visit 5 is to be performed as the end of intervention visit in case of a premature discontinuation
Eligibility assessment and randomization														
Inclusion and exclusion criteria	X	X												a) A negative urine home pregnancy test result at V1b is a prerequisite for randomization b) Recheck of all inclusion and exclusion criteria that do not require physical presence by phone at Visit 1b
Randomization		X												Randomization visit is a phone call during which site personnel inter alia informs the subject whether she is eligible
IWRS														
Study intervention (study drug, pharmacokinetics and biomarkers)														
Study intervention dispensed			X		X		X							Dispensed after a negative urine pregnancy test result
Start of study intervention			X											a) Within 8 to 15 days from the onset of menstruation that triggered Visit 2 b) The first dose to be taken at the study site
Study intervention return and accountability					X		X		X					
Blood sample for pre-dose PK			X		X				X					See Section 8.4 for further information

Procedure	Screening Period	Pre-Intervention Period[1]	Intervention Period (Days)							Follow-up Period				Notes
	28 to 70 days	8 to 35 days	1	14 ±3	28 ±3	42 ±3	56 ±3	70 ±3	84 +3	14 ±3 days after the last dose	38 ±3 days after the last dose	68 ±3 days after the last dose	90 ±3 days after the last dose	
Visit number	1a[2]	☎ (1b)	2	2a	3	3a	4	4a	5	5a	6	6a	7	Visit 5 is to be performed as the end of intervention visit in case of a premature discontinuation
Blood samples post-dose PK			X				X		X					
Blood sample for BM	X		X		X		X		X		X		X	Not relevant for China. See Section 10.2 Parameters
Blood sample for genetics			X											Not relevant for China. Only participants who consented. Can be taken also on Visit 3.
Safety-related assessments														
Physical examination	X										X		X	
Height	X													
Weight	X		X						X		X		X	
Vital signs	X		X		X		X		X		X		X	
Gynecological examination	X		X						X		X		X	
Transvaginal ultrasound	X		X						X		X		X	
Cervical cytology	X													Not needed if normal result available from test conducted within 1 year before the Visit 1a
Confirmation of preferred method of contraception	X		X		X		X		X		X		X	Options: spermicide-coated condoms, copper IUD, female sterilization, vasectomized partner(s) or abstinence
Samples for safety laboratory assessments	X		X		X		X		X		X		X	See Section 10.2

Procedure	Screening Period	Pre-Intervention Period[1]	Intervention Period (Days)							Follow-up Period				Notes
	28 to 70 days	8 to 35 days	1	14 ±3	28 ±3	42 ±3	56 ±3	70 ±3	84 +3	14 ±3 days after the last dose	38 ±3 days after the last dose	68 ±3 days after the last dose	90 ±3 days after the last dose	
Visit number	1a[2]	☎ (1b)	2	2a	3	3a	4	4a	5	5a	6	6a	7	Visit 5 is to be performed as the end of intervention visit in case of a premature discontinuation
Liver safety laboratory assessments				X		X		X		X		X		These visits are not to be performed in participants randomized to active control elagolix
Urine pregnancy test	X	X	X		X		X		X		X		X	Pregnancy test at V1b is to be conducted at home by the participant
SARS-CoV-2 virus antibody tests	X										X		X	To be performed at Visit 6 only if this is the only scheduled Follow-up visit for a participant. For further information see Section 10.2
Adverse events	X	X	X		X		X		X		X		X	Visit 5: Participants who reported taste-related AE(s) occurring during the intervention period will be asked additional questions regarding AE character
Prior and concomitant medication	X	X	X		X		X		X		X		X	
Training for pain reporting	X		X		X		X		X		X			To be performed at Visit 6 only if this is not the last Follow-up visit for a participant.

Procedure	Screening Period	Pre-Intervention Period[1]	Intervention Period (Days)							Follow-up Period				Notes
	28 to 70 days	8 to 35 days	1	14 ±3	28 ±3	42 ±3	56 ±3	70 ±3	84 +3	14 ±3 days after the last dose	38 ±3 days after the last dose	68 ±3 days after the last dose	90 ±3 days after the last dose	
Visit number	1a[2]	☎ (1b)	2	2a	3	3a	4	4a	5	5a	6	6a	7	Visit 5 is to be performed as the end of intervention visit in case of a premature discontinuation
Efficacy / patient reported outcomes assessments														
ESD, check completeness of eDiary via web report	◄	———	———	———	———	———	———	———	———	———	———	———	►	Daily data entry with eDiary device. The site personnel will be blinded to Item 1 entries prior to assessing the ESD eligibility criteria.
Dyschezia, dysuria, and hot flushes	◄	———	———	———	———	———	———	———	———	———	———	———	►	Daily data entry with eDiary device.
EIS	◄	———	———	———	———	———	———	———	———	———	———	———	►	Weekly data entry with eDiary device
EQ-5D-5L	X		X		X		X		X		X		X	Weekly on eDiary during the pre-intervention period and monthly on eDiary during the intervention and follow-up.
VAS	X		X		X		X		X		X		X	Data entry with eDiary device during visit.
PGI-S	X		X		X		X		X		X		X	Data entry with eDiary device during visit.
PGI-C					X		X		X		X		X	Data entry with eDiary device during visit.
mWPAI	X								X					Data entry with eDiary device during visit.
PSQ3			X						X					Data entry with eDiary device during visit.
PainDETECT	X		X						X		X		X	Data entry during site visits with paper questionnaire
PCS			X											Data entry during site visits with paper questionnaire

Procedure	Screening Period	Pre-Intervention Period[1]	Intervention Period (Days)							Follow-up Period				Notes
	28 to 70 days	8 to 35 days	1	14 ±3	28 ±3	42 ±3	56 ±3	70 ±3	84 +3	14 ±3 days after the last dose	38 ±3 days after the last dose	68 ±3 days after the last dose	90 ±3 days after the last dose	
Visit number	1a[2]	☎ (1b)	2	2a	3	3a	4	4a	5	5a	6	6a	7	Visit 5 is to be performed as the end of intervention visit in case of a premature discontinuation
Distribution and return of other study supplies														
eDiary device	D										R		R	Guidance for use given.
Actigraphy device	D		R				D		R					Only participants who consented. Guidance for use given.
Use of actigraphy device	◄———	———►					◄———	———►						Only participants who consented.
Standardized rescue medication	D		D		D		D		D		D			See Section 6.8.1
Spermicide-coated condoms	D		D		D		D		D		D			Guidance for use given. Re-supply as needed.

Abbreviations: AE = adverse event; BM = biomarker; D = distribution; EIS = Endometriosis Impact Scale; eDiary = electronic diary; ESD = Endometriosis Symptom Diary; EQ-5D-5L = EuroQoL 5-dimension 5-level; IUD = intrauterine device; IWRS = interactive web response system; MRI = magnetic resonance imaging; mWPAI = modified Work Productivity and Activity Impairment questionnaire; NA = not applicable; PCS = pain catastrophizing score; PGI-C = Patient's Global Impression of Change; PGI-S = Patient's Global Impression of Severity; PK = pharmacokinetic(s); R = return; VAS = visual analogue scale

2. Introduction

2.1 Study Rationale

Suspected endometriosis is treated initially with combined oral contraceptives (COCs; off-label use) or progestins mostly in combination with non-steroidal anti-inflammatory drugs. After failure of this initial drug treatment, the current gold standard treatment is the surgical ablation of the endometriotic lesions. Surgery is associated with a high recurrence rate.

Currently, there is no long-term medication available for patients in which COCs and progestins failed. The treatment with gonadotropin-releasing hormone (GnRH) agonist as second-line therapy is only approved for short term treatment (6 months), since GnRH agonists completely suppress hormonal production and are therefore associated with menopausal side-effects like bone mass loss and hot flushes. GnRH antagonists are approved in the US at the time this protocol was written. Side effects associated with the high dose, i.e., 200 mg twice daily, are comparable to those of GnRH agonists and therefore the duration of intake is also limited to 6 months. Less bone loss and hot flushes have been reported with the intake of the low dose, i.e., 150 mg/day and the treatment is limited to 2 years. Considering all available treatment modalities, recent data confirm a significant degree of unmet medical need, since up to 70% of treated patients have persistent symptoms like chronic pelvic pain that are not sufficiently managed (Bayer market research, 2009; 21,700 women in 8 countries).

This study is designed to investigate effects of three different doses of BAY 1817080, i.e., 150 mg, 75 mg and 25 mg, twice daily on endometriosis-associated pelvic pain over a 12-week intervention period in comparison to placebo and elagolix 150 mg once daily. The study encompasses the following design elements: double-blinding, randomization, active and placebo-controlled parallel group design. The study will be conducted in multiple clinical centers across Europe, North America, China, and Japan where women with symptomatic endometriosis receive medical care. The sponsor reserves the right to limit a country's participation in the actigraphy substudy to only certain countries. Such limitation will be communicated to the relevant authority at the time of submission of the study.

2.2 Background

2.2.1 Endometriosis

Endometriosis is a hormone-dependent gynecological disease characterized by painful symptoms like dysmenorrhea, chronic and non-cyclic pelvic pain and dyspareunia. Neither the etiology of endometriosis nor the precise mechanisms of the associated pelvic pain and infertility are completely understood. Also, there is no direct correlation between stage of disease, type of endometriotic lesions, and frequency and the severity of symptoms.

Pathologically the disease is defined by the presence of endometrial tissue outside the uterine cavity (endometriotic lesions). These endometriotic lesions undergo cyclical changes including bleeding and tissue remodeling and degradation. Hormonal treatments are believed to reduce proliferation of endometrial lesions by reducing estrogen activity. However, endometrial lesions also exhibit signs of inflammation. Increased concentrations of prostaglandins have been reported in peritoneal fluid of endometriosis patients and may be involved in the progression of the disease. Moreover, various processes that can lead to

release of ATP play an important role in the disease pathophysiology of endometriosis. Besides inflammation itself, mechanical stretch due to displaced tissue growth or e.g. peritoneal adhesions as well as movement and distension contribute to processes that lead to the release of ATP, which is suggested to play a dominant role in nociception and neurogenic inflammation (2, 3); for review see (4, 5).

2.2.2 BAY 1817080

The P2X3 receptor belongs to the P2 receptor family that is activated by purine and pyrimidine nucleotides and can be subdivided into ionotropic P2X receptors and metabotropic P2Y receptors based on their molecular properties. Among the P2X family members, in particular P2X3 (natural ligand ATP) has been recognized as an important mediator of nociception and other disorders with an over-activation of sensory nerve fibers including genitourinary, gastrointestinal and respiratory conditions (6-9).

While the expression of P2X3 in sensory neurons of dorsal root ganglions has been extensively described, the presence in nerve fibers of endometriotic lesions has only been recently described (10) and was confirmed by the sponsor (See IB for further information).

These characteristics together with the role of P2X3 in neurogenic inflammation present a novel disease mechanism in endometriosis that could combine a high efficacy on pain together with an innovative mechanism of action for disease modification.

BAY 1817080 has been identified as a human P2X3 receptor antagonist discriminating between the P2X3 homomer and the P2X2/3 heteromer. Secondary *in vitro* assays revealed a high functional potency on rat P2X3 and P2X2/3 receptors.

BAY 1817080 showed robust effects on complete Freund's adjuvant-induced pain after oral administration in *in vivo* studies in rats and mice and almost completely reversed neurogenic inflammation back to vehicle levels in rats, demonstrating experimentally that blocking P2X3 addresses this mechanism.

BAY 1817080 significantly reduced dyspareunia in a rat endometriosis model. The study revealed a sustained effect which was still observed one week after treatment cessation.

Taken together, BAY 1817080 demonstrated robust efficacy in different *in vivo* and *in vitro* models including effects on neurogenic inflammation with high relevance for endometriosis.

2.3 Benefit/Risk Assessment

Relevant emerging safety data, e.g., SAEs, SUSARs, and serious safety-related protocol deviations, will be communicated as soon as possible between the sponsor, all study sites and investigators and trial subjects according to the requirements of the European Medicines Agency guideline on strategies to identify risks for First in Human and Early Clinical trials. For a detailed description of the communication process see to Section 10.3.4.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of BAY 1817080 may be found in the IB, and for the comparator elagolix in the package insert.

BAY 1817080 is believed to carry the potential to relieve pain and improve quality of life of patients with endometriosis. Target engagement of BAY 1817080 has been demonstrated in a

Phase 2a study in patients with recurrent and/or unexplained chronic cough, i.e., efficacy was demonstrated in this patient population (study 18184, see the latest available version of the IB).

Taste-related AEs which were reported as mild and reversible upon cessation of treatment were assessed as an identified risk which will be monitored.

The benefit/risk ratio for BAY 1817080 is considered favorable for the planned study.

2.3.1 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention BAY 1817080		
Taste-related AEs	To date, the influence of BAY 1817080 on taste perception has been investigated in a limited number of study participants only and was reported as non-serious and mild. Changes were fully reversible after the end of treatment with BAY 1817080. No participants discontinued the treatment because of taste disturbances. Study 18184 (11) was a two-part study, investigating safety and PK of BAY 1817080 in healthy volunteers (Part 1) and safety, efficacy and PK in patients with refractory chronic cough (Part 2). In Part 1, the frequency of the taste-related AEs was evenly distributed between participants receiving active treatment with BAY 1817080 (3 participants; 8.6%) and participants receiving placebo (1 participant; 8.3%). In Part 2 of study 18184, overall 10 out of 40 participants treated reported a taste-related AE. Some of the AEs lasted for two or more consecutive treatment intervals with different doses. There was a dose-dependent frequency increase of taste-related AEs from 5.1% of participants reporting the AE at the lowest dose to 20.5% at the highest dose (corresponding to the 150 mg BID given in this trial). Taste-related AEs were reported by 2.5% of participants receiving placebo. At this stage of clinical development taste disturbance is regarded an identified risk.	In this study, the frequency of taste-related AEs will be evaluated, including the assessment of how bothersome the AEs are perceived to be.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Antithrombin III activity increase	In study 18184 (11) (Part 1), ATIII activity increases were observed in healthy participants treated with 200 mg and 750 mg BID of BAY 1817080 . Effect was first observed 3 days after the first dose. Increase was up to ~20% above baseline in the 200 mg BID group, and up to ~30% above baseline in the 750 mg BID. In study 18184 (Part 2), in patients with refractory chronic cough, there were similar time and dose-dependent increases of ATIII activity observed as in the healthy volunteers in Part 1 of the study. No changes in coagulation parameters were observed and no signs of bleeding/ bruising related to BAY 1817080 were observed in study 18184 or other studies, to date, with BAY 1817080. Furthermore, there is no established clinical relevance linked to increased ATIII activity in medical literature. Therefore, it is concluded that at this stage of development, the increase in ATIII activity can be considered as not clinically relevant. Increased antithrombin III activity at this stage of development is regarded a potential risk.	ATIII activity will be measured in this study. Coagulation parameters prothrombin time (Quick), aPTT, fibrinogen, and INR will be monitored regularly during the study as part of safety laboratory assessments. Study participants will also be monitored for signs of bleeding and bruising during the planned physical examinations.
Potential decrease in heart rate and diastolic blood pressure	In study 18184, a decrease in DBP (4-7 mmHg) and HR (5-11 bpm) was observed in the highest dose group (Part 1; mainly in 2-3 participants with high baseline values). The decrease in DBP and HR was not observed in patients with refractory chronic cough (Part 2). In the absence of AEs related to the changes in DBP and HR, such as dizziness or syncope, this observation was considered as not clinically significant. Decrease in HR and DBP at this stage of development is regarded as a potential risk.	HR and blood pressure will be monitored in this study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential changes in liver function laboratory parameters	Inhibition of bile salt transport in the liver is linked to an increased risk of DILI. Eliapixant was not an inhibitor of bile salt transporter BSEP in an in vitro assay in human hepatocytes up to concentrations of 300 µM, although inhibition of BSEP in a vesicle assay only expressing human BSEP was detected. In dogs, findings on the liver included elevated enzymes at the high dose (mainly GLDH and ALT, without relevant effects on total-bilirubin) in individual animals in the subchronic and chronic studies (up to 39 weeks) without an apparent histopathological correlate. No relevant increase in bile acid concentration was observed in the multiple dose escalation phase 2a study 18184 in humans. No relevant change in liver related parameters was seen in Study 18183 and Study 18184 after administration of eliapixant, both in healthy volunteers and participants with chronic cough (12). As of 16 DEC 2021, four cases of increased transaminases are reported in the ongoing phase II program (two in study 20393, refractory and/or unexplained chronic cough, one in study 19733, overactive bladder, and one in study 20584, endometriosis) investigated by close liver observation as described in the FDA DILI guidance (13) and in this study protocol. There has been one serious case of moderate hepatocellular liver injury, seen 4 weeks after start of treatment in study 20393, with the study drug as most likely cause. This patient was administered 150 mg of eliapixant (BID). The PPD female study participant reported nausea and vomiting starting approx.14 days after start of treatment with the study drug. She presented with ALT of 9.3-fold ULN AST of 4.6-fold ULN at the regular visit after four weeks of treatment with the study drug, after normal values being recorded at screening. Treatment with study drug was discontinued immediately. ALT peaked at 19.9-fold ULN three days after discontinuation of study drug, AST reached the 14.9 fold ULN at the same time, serum bilirubin levels peaked at 1.6 fold ULN. The detailed workup on alternative causes of this patient's liver injury did not reveal a conclusive	Liver-specific exclusion criteria and discontinuation rules have been defined. Liver function laboratory parameters will be assessed at 2-weekly intervals. Investigators and participants should pay special attention to non-specific symptoms which may be associated with liver dysfunction, including anorexia, nausea, fatigue, right upper abdominal discomfort, vomiting, malaise, jaundice, fever, and rash. Information on these symptoms should be asked for in case of abnormal liver laboratory values (see Section 10.6.2) or any other suspicion of liver dysfunction. The study participants should be reminded to contact the study site immediately, if they are concerned about such symptoms and unscheduled liver laboratory assessments should be considered. In addition, study participants will be instructed to limit alcohol consumption while participating in the study

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	alternative cause. The patient recovered from increase in transaminases as well as from nausea and vomiting, total bilirubin also returned to normal. There were two cases of mild ALT increase above the threshold of 3-fold ULN, one in the refractory and/or unexplained chronic cough study 20393, the other one in the overactive bladder study 19733. Eight weeks after start of treatment, the ALT values in these female participants peaked at 3.9-fold ULN and 3.1-fold ULN, respectively. The patient from study 20393 received 75 mg of eliapixant BID, the treatment information for the patient in the overactive bladder study 19733 is still blinded. Both participants were asymptomatic with regard to signs or symptoms suggestive of liver disease. For both cases, transaminases started to decrease under ongoing treatment with the study drug. The patient in study 20393 decided to stop treatment before the 12-week-visit and reached normal values during the 4-weeks follow-up period, approx. two months after the maximum ALT increase. The other patient recovered under treatment, transaminase values returned to normal approx. four weeks after the maximum elevation. These two cases did not meet the biochemical criteria for liver injury according to the criteria defined by DILI Expert Working Group (13, 14). The 4th case, a moderate liver injury of hepatocellular pattern, occurred in study 20584. The patient complained about malaise about 3 weeks after start of treatment with the study drug. An increase in ALT of 7.5-fold ULN and of 3.9-fold ULN in AST was diagnosed at week 4 after start of treatment with eliapixant. Close liver observation revealed that this patient was positive for Anti Hepatitis A Virus IgM at baseline and at least until 6 weeks after start of treatment. However, no HAV RNA was detected in serum at any point in time, and until 11 weeks after the first finding of anti-HAV IgM antibodies, also no anti-HAV IgG antibodies were detected, what would be expected during the typical course of a HAV infection. The totality of data gathered to clarify the causality of this case do not support a recent acute infection by hepatitis A virus. In conclusion, the case was assessed as an acute hepatocellular liver injury of moderate severity considering the associated symptoms.	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	The suggestive chronology and the absence of clearly potential other causes make eliapixant the most probable cause. The study drug was stopped immediately, the transaminases returned to normal values. Changes in liver function values at this stage of development are regarded as a potential risk.	
Reproductive toxicity	Studies on reproductive and developmental toxicity of BAY 1817080 were conducted in rats and rabbits. No effects of BAY 1817080 on male/female reproduction, fertility or developmental toxicity have been detected with multiples of exposures relative to the anticipated human therapeutic exposures of about 6-fold (rats) and 0.8-fold (rabbits). In the absence of findings with BAY 1817080, the CTFG guideline (15) recommends use of at least 'acceptable effective' methods of contraception in clinical trials with women of childbearing potential.	For this study, barrier contraception in the form of spermicide-coated condoms (supplied by the sponsor) is considered to be practically the only commonly used and hence feasible method of contraception (for reasons outlined below). Hormonal contraception ('highly effective' methods of contraception per CTFG guideline (15)) would interfere with efficacy study endpoints. The following methods of contraception are allowed in addition to barrier contraception (spermicide-coated condoms): copper IUD (placed at least 6 months before visit 1a); total sexual abstinence; tubal-ligation; vasectomized partner. To minimize the risk of pregnant women entering the intervention phase, intervention will only be started following menstruation and a negative urine pregnancy test, to be further confirmed by a serum pregnancy test. Urine pregnancy tests will be conducted at every visit after start of intervention (home urine pregnancy testing kits are centrally distributed. A pregnancy test is to be taken every 4 weeks).
Active Comparator Elagolix (16)		
Elagolix is contraindicated in women who are pregnant, with known osteoporosis, with severe hepatic impairment, and with concomitant use of strong OATP 1B1 inhibitors (e.g., cyclosporine and gemfibrozil). The following warnings and precautions apply:		
Bone loss	Bone mineral density loss is greater with increasing duration of use and may not be completely reversible after stopping treatment.	Specific exclusion criteria have been defined, i.e., women with known osteoporosis and a history of low-trauma fracture are excluded.
Change in menstrual bleeding pattern and reduced ability to recognize pregnancy	Reduction in the amount, intensity or duration of menstrual bleeding	Pregnancy testing performed in a regular manner
Suicidal ideation, suicidal behavior, and exacerbation of mood	Higher incidence of depression and mood changes compared to placebo in clinical trials	Patients with new or worsening depression, anxiety or other mood changes should be referred to a mental

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
disorders		health professional, as appropriate. Advise patients to seek immediate medical attention for suicidal ideation and behavior.
Hepatic transaminase elevations	In clinical trials, dose-dependent elevations of serum ALT at least 3 times the upper limit of the reference range occurred	Liver-specific exclusion criteria and discontinuation rules have been defined. Liver function laboratory parameters will be assessed at 4-week intervals. Please refer to elagolix prescriber information for more information
Study Procedures		
Participation in this study presents a minimal risk as the documented AEs observed in prior studies were mild and completely resolved.	Frequent blood sampling (by single vein puncture and/or indwelling cannula) may be accompanied by mild pain, hematoma, feeling faint or dizzy, and in rare cases inflammation of the vessel wall or injury of a nerve. Collection of a cervical smear may be associated with discomfort and spotting. Participants may experience discomfort and pain while a transvaginal ultrasound is performed. A transrectal ultrasound is in addition associated with the risk of bowel perforation and bleeding.	All study assessments will be carried out by trained clinical staff.

2.3.2 Benefit Assessment

Administration of BAY 1817080 may be associated with the following benefits

- may lead to relief of pain symptoms with long-term benefit, which is expected to be associated with increased quality-of-life and social functioning
- may have disease modifying activity by attenuating neurogenic inflammation
- may prolong the intervals between laparoscopic interventions due to the improvement of symptoms, thereby reducing the overall amount of surgical interventions needed
- is expected to have no impact on the menstrual cycle

Hence there is a potential benefit in developing BAY 1817080 for patients with endometriosis. However, to date only preclinical evidence supports this notion (animal data demonstrated that BAY 1817080 blocks neurogenic inflammation and attenuates inflammatory pain). Accordingly, study 20584 is the first to assess clinical efficacy of BAY 1817080 in patients with endometriosis.

2.3.3 Overall Benefit-Risk Conclusion

Considering one confirmed and one potential case of DILI in patients exposed to BAY 1817080 for 8-12 weeks of treatment during the phase 2 program in all indications, the benefit-risk ratio of BAY 1817080 is no longer considered to be positive.

3. Objectives, Endpoints and Estimands

Objectives	Endpoints
Primary	
• To assess the dose-response relationship and demonstrate efficacy of BAY 1817080 compared to placebo in women with symptomatic endometriosis	• Absolute change in mean worst EAPP from baseline[3] to end of intervention[4] (measured daily on the NRS by item 1 of the ESD)
Secondary	
• To identify at least 1 superior effective dose of BAY 1817080 compared to placebo • To evaluate the safety and tolerability of 3 doses of BAY 1817080 compared to placebo and elagolix 150mg in women with symptomatic endometriosis	• Absolute change in mean worst EAPP from baseline[3] to end of intervention[4] (measured daily on the NRS by item 1 of the ESD) • Number of participants with treatment emergent adverse events
Other pre-specified	
• Assessment of efficacy of BAY 1817080 compared to placebo and elagolix 150mg in the treatment of EAPP at weeks 4 / 8 and end of intervention period • Assessment of efficacy of BAY 1817080 compared to placebo and elagolix 150mg in the treatment of EAPP during days with vaginal bleeding (dysmenorrhea/menstrual pelvic pain) at weeks 4/ 8 and end of intervention period • Assessment of efficacy of BAY 1817080 compared to placebo and elagolix 150mg in the treatment of EAPP during days without vaginal bleeding ('non-menstrual pelvic pain') at weeks 4 / 8 / and of intervention period • To further describe the patient population, efficacy profile of BAY 1817080 and change during the study period using the data collected by patient reported outcomes (see Section 8.1.1)	• Absolute change in mean worst EAPP from baseline[3] to the first 4 weeks/ 8 weeks of intervention[5]/end of intervention[4] (measured daily on the NRS by item 1 of the ESD) • Absolute change in mean worst EAPP on bleeding days from baseline[3] to the first 4 weeks/ 8 weeks of intervention[5]/end of intervention[4] (measured on the NRS by item 1 and item 4 of the ESD) • Absolute change in mean worst EAPP on non-bleeding days from baseline[3] to the first 4 weeks/ 8 weeks of intervention[5]/end of intervention[4] (measured on the NRS by item 1 and item 4 of the ESD) • Item level, total and/or domain scores at screening, baseline, weeks 4/8/end of intervention and absolute change from baseline, as applicable

[3] Baseline: Last 28 days before start of the intervention visit

[4] End of Intervention: Last 28 days of the treatment period, Day 57 - 84 (+3)

[5] 28 days of the intervention period: Day 1-28 / 29-56, respectively

Objectives	Endpoints
• To assess sustainability of treatment effect and recurrence of symptoms	• Absolute change in mean worst EAPP (overall, during and outside days with vaginal bleeding) from end of intervention[4] to non-overlapping, consecutive 28-day intervals during follow-up (measured daily on the NRS by item 1 of the ESD) • Details of the endpoints on other symptoms will be described in the SAP
• Other endpoints not mentioned as primary, secondary, biomarker or pharmacokinetic endpoint	• Details will be described in the SAP
Other pre-specified: biomarkers	
• To further investigate the study intervention and similar compounds (e.g., mode-of-action-related effects, safety) and to further investigate pathomechanisms deemed relevant to endometriosis and associated health problems	• Various biomarkers (e.g., diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)
• To evaluate potential associations between disease-associated genotypic information and clinical efficacy and /or pharmacodynamic effects	• Exploration of potential differential safety or efficacy in the presence or absence of genetic polymorphisms
• Support of the development of a blood-based diagnostic test for endometriosis	• Measurement of panel of blood-based candidate biomarkers hypothesized to be diagnostic for endometriosis
• To examine sleep quality and activity as a response marker for intervention	• Actigraphy (e.g. total minutes asleep, sleep effectiveness, sleep latency, awakenings) by a wrist monitoring device worn for up to 30 days before and during intervention
Other pre-specified: pharmacokinetics	
• To investigate pharmacokinetics of BAY 1817080 in patients with endometriosis	• Systemic exposure of BAY 1817080 via sparse PK sampling in patients with endometriosis

Primary efficacy variable

The primary efficacy variable will be the absolute change in mean worst EAPP from baseline (last 28 days before the first intake of study drug) to end of intervention (last 28 days ending with the last intake of study drug planned on Day 84 (+3)).The worst EAPP will be measured daily on the NRS by item 1 of the ESD. The time frame of 28 days captures a menstrual cycle on average.

Intercurrent events

Details on the incorporation of intercurrent events (ICEs) considered as treatment failure/success and as such addressed by the composite strategy will be provided in the SAP. These ICEs are premature discontinuation of study treatment due to a non-COVID-19-related AE and a premature discontinuation of study treatment due to lack of efficacy.

Increased and decreased intake of standardized rescue medication taken for EAPP will be addressed by the treatment policy strategy. One argument to consider standardized rescue medication as part of the treatment is its availability over the counter. On the other hand, a

higher/lower need for rescue medication is a sign of treatment failure/success that is not or only partly reflected in the worst EAPP. Since a novel approach is considered to apply the composite strategy, this strategy will be used in supplementary analyses. Earlier trials (outside from the US) suggest that a primary analysis using the treatment policy strategy will likely not be overly conservative. The observed intake of standardized rescue medication taken for EAPP was generally low.

Any change in intake of standardized rescue medication taken for other reasons than EAPP is considered as part of a general treatment. Consequently, the treatment policy strategy will be used. Thus, standardized rescue medication is part of the treatment attribute described below.

Premature discontinuations due to the COVID-19 pandemic, i.e. participant's pandemic-related inability or unwillingness to continue due to an actual COVID-19 infection, including related AEs, or other/administrative reasons or pandemic-related administrative reasons on site level, will be addressed by the hypothetical strategy. The affected participants are assumed to have similar outcomes to completers. Details will be provided in the SAP.

In the spirit of the hypothetical strategy, EAPP values that are missing while a confirmed COVID-19 infection is classified as severe AE will be considered Missing at Random and modelled based on participant's EAPP observed on days with no severe COVID-19 infection.

The impact of other potential ICEs (e. g. death of any cause, including COVID-19 infection, pregnancy, or surgery) is expected to be negligible, even in total. If a blind review will show an unexpected high number, the definition of the primary estimand may be complemented in the SAP.

Remaining attributes of the primary estimand

The treatments will be BAY 1817080 25 mg or 75 mg or 150 mg or placebo each, plus standardized rescue medication taken for any reason.

The target population is defined by the inclusion/exclusion criteria described in section 5 restricted to non-Chinese participants with surgically -confirmed endometriosis.

The population-level treatment group summary is the estimated model-based group mean of the primary variable's values adjusted for region (Japan vs. ROW excluding China) and baseline EAPP. Treatment effect will be evaluated as difference between group means.

4. Study Design

4.1 Overall Design

- **Study design summary:** Multicenter, randomized, placebo- and active comparator controlled, double blind to placebo and open-label comparator; parallel group
- **Intervention group:** Parallel
- **Study duration:** Maximum of 233 days (Follow-up 1: subjects with 38±3 days follow-up) or 285 days (Follow-up 2: subjects with 90±3 days follow-up)
- **Intervention duration:** 84 days (+3 days)

- **Study Periods:**
  - Screening
  - Pre-intervention
  - Intervention
  - Follow-up
- **Diagnosis group:** Endometriosis

Approximately 840 participants will be screened to start study intervention in about 420 randomized participants for at least 50 participants evaluable for the primary analysis (i.e. included in the pPPS) per intervention group. The primary analysis will not include the participants enrolled based on visually-confirmed diagnosis, i.e. about half of the women randomized in Japan, nor the participants randomized in China, who are mainly included to generate further data using the ESD in this population. Refer to Section 9.3 for further information of inclusion of participants into analysis sets.

Screening period

The duration of the screening period should be kept to a minimum. Investigators are advised to schedule screening visit during the 2nd half of the menstrual cycle, ideally closely before the next menstrual bleeding, to minimize the time in the screening period. In rare cases of technical issues it may not be feasible to complete the screening within 70 days. In these cases the screening period may be extended over 70 days with prior approval from Sponsor, on case by case basis.

Daily ESD completion will begin from Visit 1a. The 28-day assessment period for ESD eligibility criteria (see Section 5.1) starts from Day 1 of the first menstrual bleeding on or after Visit 1a (Day 1 of the menstrual cycle is defined as the first of the 2 consecutive days with more than spotting).

Randomization

Participants who fulfill all eligibility criteria will be randomized at Visit 1b in a ratio of 1:1:1:1:1 into one of the 5 treatment groups:

- Treatment group 1: 150 mg of BAY 1817080 BID
- Treatment group 2: 75 mg of BAY 1817080 BID
- Treatment group 3: 25 mg of BAY 1817080 BID
- Treatment group 4: placebo
- Treatment group 5: elagolix 150mg QD

Participants from Japan and China will be randomized to treatment groups 1 through 4.

The chosen stratification factors are region (China, Japan and rest of the world) and type of diagnosis (surgically vs clinically [for Japanese participants only]).

Pre-Intervention period

The duration of the pre- intervention period should be kept to a minimum. In rare cases it may not be feasible to complete the pre-intervention period within 35 days. In these cases the pre-intervention period may be extended over 35 days with prior approval from Sponsor, on case by case basis.

Double-blind Intervention Period

The randomization and the start of intervention will take place on two different visits in order to supply the study drug per shipment on demand. To have a synchronized start of intervention with menstrual cycle, Visit 2 should be scheduled between Day 8 and Day 15 of the menstrual cycle.

Intervention period for primary analyses is 84+3 days.

Follow-up Period

The follow-up period will last for at least 90 days (13 weeks) for all study participants randomized to blinded treatment. Participants randomized to the open label elagolix arm will have a follow-up period of at least 38 days (5 weeks) after the last dose of study intervention.

Interim Analysis

Interim analyses may be performed after approximately 50% of the study participants have completed the 12-week intervention period in order to plan subsequent studies.

4.2 Scientific Rationale for Study Design

Study population

The study objective is to investigate whether treatment with BAY 1817080 is associated with relief from EAPP. Eligible participants must have been diagnosed with endometriosis and experience moderate to severe EAPP. Participants with mild EAPP are not included as they are considered to have lower medical need. In addition, potential floor effects may preclude identification of therapeutic effects of BAY 1817080 in participants with low pain scores.

Adolescents/ minors are excluded due to the limited clinical experience with BAY 1817080. No upper age limit is defined since the requirement for menstrual bleedings during the screening period limits the population to premenopausal women. Peri-/menopause is typically entered at age between 40 and 55 years. Hence elderly participants will not be included.

Participants need to be legally able to consent themselves.

Choice of the primary variable

Participants with endometriosis report pelvic pain as a key symptom. It is commonly the reason for presentation to the physician. Accordingly, a primary endpoint assessing pelvic pain is suitable.

Daily worst pain measurements using NRS are used to assess EAPP. Worst pain recording with a 24-hour recall period (ESD) has been successfully used in previous therapeutic studies (17, 18). The pain threshold for inclusion in this study is identical to the one used in two previous endometriosis studies (sum NRS score of ≥98 over 28 days (17, 18).

In addition to the daily ESD measurements complemented by application of visual analogue scale, VAS (4-week recall period) will be completed, for comparison with historic data.

Study periods

Screening period is needed for the assessment of pain level in the absence of hormonal treatments (daily pain recordings, ESD). The maximum duration of the screening period is driven by the following consideration:

- time required for stopping use of oral contraceptives after Visit 1a
- repetition of ESD eligibility assessment based on menstrual bleeding, if required

Intervention period of 84 days was chosen to cover at least two menstrual cycles. The maximum intervention duration covered by animal toxicology is 90 days.

A follow-up period of at least 35 days was chosen to cover at least one menstrual cycle for most of the participants while also offering the possibility to assess sustainability of the assumed therapeutic effect of BAY 1817080. In about 50% of randomized participants the follow-up period is extended to 90 days to generate further data on sustainability of the assumed treatment effect.

Dose

See Section 4.3 for justification of the selected dose.

Placebo control and standardized rescue medication

Placebo effects have been observed in previous endometriosis studies using patient-reported outcomes as endpoints. The size of the placebo effect varies across studies. While causes of the observed variability are not fully understood, the size of placebo effect is associated with expectations of participants, type of rescue medication provided and study design (e.g. larger effects in studies with active control than in placebo-controlled studies or inclusion/exclusion criteria that introduce regression towards the mean). Accordingly, a placebo-controlled design is considered scientifically necessary to differentiate drug effects from the natural course of the disease and placebo effects.

In two studies (17, 18) with similar provision of rescue medication (ibuprofen), the rate of early discontinuations was in the range typically encountered in clinical trials (approximately 20-30%). Based on the randomization ratio (see Section 4.1), it is planned that approximately 4 of 5 participants (80%) will receive active intervention. In summary, use of a placebo control is considered justified and feasible.

Active comparator

The active comparator elagolix 150mg will be provided open label as blinding was not possible due to technical reasons.

Blinding

Blinding of study participants for BAY 1817080 is considered appropriate because endpoints based on reporting by participants and/or physicians might be influenced by the knowledge about the intervention received.

Contraception

The rationale for the methods of contraception permitted during study participation is outlined in the benefit-risk assessment (see Section 2.3).

4.3 Justification for Dose

This dose finding study aims to generate first evidence of efficacy of the P2X3 antagonist BAY 1817080. Specifically, this study is designed to investigate effects of three different doses of BAY 1817080, i.e., 150 mg, 75 mg and 25 mg, twice daily on endometriosis-associated pelvic pain over a 12-week intervention period in comparison to placebo and elagolix 150 mg once daily.

In this study, the doses were selected based on the following:

- The selected dose should result in sufficiently high exposures that blocks the target to an extent, which allows to conclusively confirm or refute the hypothesis that targeting P2X3 translates into pain relief for patients with endometriosis and to determine the optimal dose to be tested in the subsequent confirmatory Phase 3 trials in this population.
- The safety/ tolerability profile based on clinical evidence gathered to date should ensure participants' safety during trial participation and reduce the risk of early discontinuations due to adverse events or perceived lack of efficacy.

For BAY 1817080, the above-mentioned criteria are fulfilled for the selected doses of 75 and 150 mg BID[6]:

- Based on current dose predictions from preclinical studies and data from the proof of concept study in patients with refractory and/or unexplained chronic cough (study 18184), the lowest fully effective dose was observed at a dose of 200 mg BID with formulation A[7]. Exposures after dosing of 200 mg BID with formulation A correspond to exposures expected with ~75 mg BID with formulation B. In this study, formulation B is used.
- The doses of 25 mg, 75 mg and 150 mg BID were chosen in order to allow investigating the full dose response on endometriosis-associated pelvic pain, i.e., testing one lower, partially effective dose of 25 mg and one higher, also fully effective dose of 150 mg BID (formulation B). The doses of 25 mg, 75 mg and 150 mg BID of formulation B are expected to be similar in terms of systemic exposure to the doses of 50 mg, 200 mg and 750 mg of formulation A previously tested in Phase 2a (see Figure 4–1).
- Expected exposures after administration of 25 mg, 75 mg and 150 mg BID of BAY 1817080 are believed to be sufficient to conclusively investigate the dose response in patients with symptomatic endometriosis.

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6 Formulation B (formulation A is an immediate release tablet, which was used in Phase 1 studies, while formulation B is a solid dispersion tablet [see the latest available version of the IB for further details])

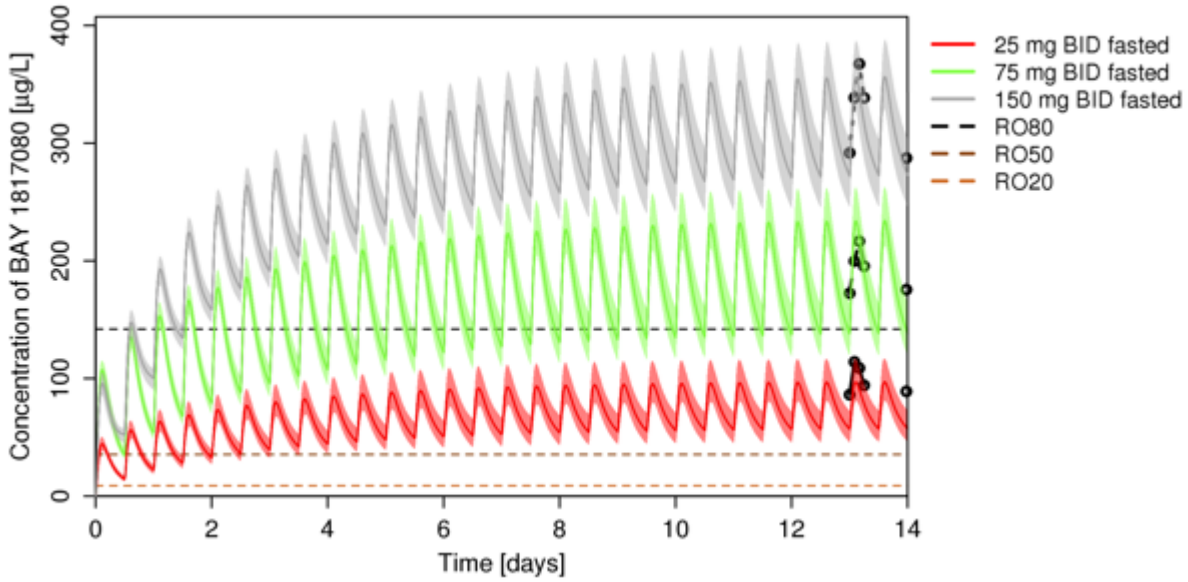
7 Clinical proof of target engagement is derived from the proof of concept study with BAY 1817080 in patients with refractory and/or unexplained chronic cough (study 18184; see the latest available version of the IB). For patients who had received the maximum technically feasible dose of 750 mg BID or the next lower dose of 200 mg BID, awake cough counts were reduced on top of placebo by 24.4% and 26.1% , respectively.

- In study 18184, the highest exposure (after multiple doses of 750 mg of formulation A) was found to be well tolerated and safe (see the latest available version of the IB for further details). 750 mg BID of formulation A translates into approximately 150 mg BID of formulation B in terms of systemic exposure. Accordingly, exposures following administration of 25 mg, 75 mg and 150 mg BID of formulation B are expected to be similar to the concentrations covered in the multiple dose study 18184 (see the latest available version of the IB and Figure 4–1 below; applies to both fasted and fed state).
- In study 19519, a 400 mg single dose of formulation B was found to be safe. Study 19519 assessed bioavailability after administration of single doses of formulations A and B of BAY 1817080 in healthy young males (see the latest available version of the IB).

Therefore, there are no anticipated safety concerns with the selected doses of 25 mg, 75 mg and 150 mg BID of BAY 1817080 in study 20584. Tolerability is expected to facilitate completion of the study by the required number of participants and accordingly interpretation of study results (i.e. rate of early discontinuations within expectations).

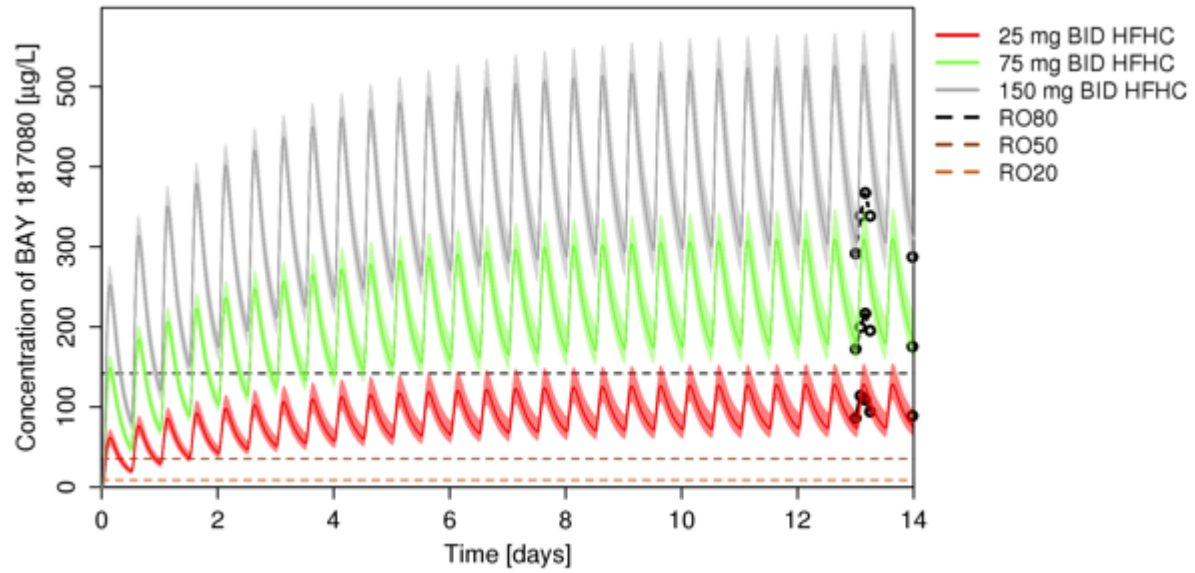
Figure 4–1: Model-Based Predicted Average Concentrations After Administration of 25 mg, 75 mg and 150 mg BID of BAY 1817080 Formulation B

A)



Model-based predicted average concentrations (including 95% confidence interval) after multiple dose administration (BID) of 25 mg, 75 mg and 150 mg of BAY 1817080 formulation B given fasted, in comparison to the geometric mean concentrations (steady-state, BID) observed in study 18184 Part 2 with 50 mg, 200 mg and 750 mg of formulation A (black circles & black lines). 75 mg: based on 25 mg fasted model.

B)



Model-based predicted average concentrations (including 95% confidence interval) after multiple dose administration (BID) of 25 mg, 75 mg and 150 mg of BAY 1817080 formulation B given fed (high fat, high calorie meal), in comparison to the geometric mean concentrations (steady-state, BID) observed in study 18184 Part 2 with 50 mg, 200 mg and 750 mg of formulation A (black circles & black lines). 75 mg: based on 100 mg fed model.

Abbreviations: BID = bis in die (twice daily); HFHC = high fat, high calorie; RO = receptor occupancy

4.4 End of Study Definition

A participant is considered to have completed the study if she has completed all phases of the study including the last visit (Visit 6 or Visit 7, respectively).

The primary completion is defined as the date of the end of intervention visit (Visit 5) of the last participant in the study globally.

The end of the study is defined as the date of the last visit of the last participant in the study globally.

5. Study Population

Women with symptomatic endometriosis meeting all inclusion criteria and presenting none of the exclusion criteria will be eligible for randomization.

Prospective approval of protocol deviation to inclusion and exclusion criteria, also known as protocol waiver or exemption, is not permitted.

5.1 Inclusion Criteria

Participants are eligible only if all of the following criteria apply:

Age

1. Participant must be ≥ 18 years of age at the time of signing the informed consent

Type of Participant and Disease Characteristics

2. Visually-confirmed endometriosis: detection of endometriotic lesions during laparoscopy or laparotomy (with or without pathological diagnosis) within 10 years but no less than 8 weeks from Visit 1a (surgically diagnosed endometriosis).
   For Japan only and limited to no more than half of all randomized Japanese participants: the diagnosis can be based on previous imaging (i.e. endometriosis lesion detected by ultrasound or MRI). If the participant was diagnosed by ultrasound, the lesion must be visualized again by ultrasound at the screening visit. If the participant was diagnosed by MRI, the diagnosis must have been made within 12 months before Visit 1a (clinically diagnosed endometriosis).
3. Both sub-criteria regarding pain symptoms must be fulfilled:
   - At Visit 1a, participant presents self-reported moderate to severe pain which – based on the judgement of the investigator – carries a reasonable likelihood to translate into a severity of pain symptoms sufficient to fulfil the eligibility criterion and be caused by endometriosis, and
   - During the screening period at least 24 daily ESD entries during the 28 consecutive days starting on the first day with menstrual bleeding at or after Visit 1a and entries in the ESD item 1a (‘worst pain’ on the daily numerical rating scale) sum up to 98 or more.

4. Willingness to use standardized rescue pain medications for EAPP (i.e. ibuprofen, acetaminophen and tramadol) and not use any prophylactic pain medication, according to investigator's instruction
5. Ability to swallow the study intervention, i.e., the different kinds of tablets, as complete units
6. Good general health (except for findings related to endometriosis) as proven by medical history, physical and gynecological examinations and laboratory test results
7. Normal or clinically insignificant cervical cytology not requiring further follow-up:
    - A cervical cytology sample has to be obtained during screening, or
    - A documented normal result has to be available from cervical cytology conducted within 12 months prior to Visit 1a.
    - Human papilloma virus (HPV) testing in participants with atypical squamous cells of unknown significance (ASCUS) will be used as an adjunctive test automatically. Participants with ASCUS can be included if they are negative for high-risk HPV strains.

Sex

8. Female

    Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

    Participants must be willing to use a non-hormonal barrier method for contraception (spermicide-coated condoms for their partners) from screening visit until the end of the study. This is not required if adequate contraception is achieved by vasectomy of the male partner(s), female sterilization, use of copper IUD for at least 6 months or total abstinence from heterosexual intercourse (for details refer to section 10.4).

Informed Consent

9. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol

5.2 Exclusion Criteria

Participants are to be excluded from the study if any of the following criteria apply:

Medical Conditions

1. Current pregnancy or less than 3 months since delivery, abortion or stop of lactation before Visit 1a
2. Hypersensitivity to any ingredient of the study intervention and/or the standardized rescue medications (see the latest available version of the IB for BAY1817080 and placebo, and the prescriber information for elagolix and the standardized rescue medications)
3. Known osteoporosis

4. History of a low trauma fracture
5. Contraindications for elagolix or the standardized rescue medications
6. Current malignancy or history of cancer (exception: basal cell or squamous cell carcinoma of the skin) within the last 5 years prior to Visit 1a
7. Any other disease or condition that, according to the investigator, can compromise the function of the body systems and could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the study intervention (e.g., extremely low body weight, chronic bowel diseases, Crohn's disease and ulcerative colitis)
8. Menopause or signs of menopausal transition, such as absence of regular menstrual cycles based on investigator's judgment (absence of information regarding menstrual bleeding pattern e.g. due to long term use of hormonal contraception is not an exclusion criterion)
9. Any disease or condition that may worsen during the study period according to the assessment and opinion of the investigator
10. Abnormal uterine bleeding in terms of regularity or heaviness (with the exception of heavy menstrual bleeding that does not require treatment)
11. Any findings that require further diagnostic procedures to avoid harm to the participant (e.g. ovarian tumors of uncertain origin or pelvic masses of unclear etiology)
12. Any serious or unstable diseases or medical conditions, including psychiatric disorders, that might interfere with the conduct of the study or the interpretation of the result, including for example:
    - history of hysterectomy and/or bilateral oophorectomy
    - any conditions considered to contribute significantly to pelvic pain by the investigator, e.g. fibromyalgia, uterine fibroids, irritable bowel syndrome or other bowel disorders
    - any other underlying diseases requiring regular use of pain medication (e.g. migraine)
    - history of or current anxiety or depression unless stable with or without medical treatment ≥ 6 months before Visit 1a
13. Major surgery scheduled during the study period
14. Non-responsiveness of EAPP to earlier treatment with GnRH-agonists or GnRH-antagonists, based on the judgement of the investigator
15. SARS-CoV-2- positive virus RNA test within 4 weeks prior to Visit 1a reported by participant, regardless of whether the participant had symptoms.
16. History of COVID-19 infection with persistent/ongoing symptoms
17. Contact with SARS-CoV-2- positive or COVID-19 patient within the last 4 weeks prior to Visit 1a

Prior/Concomitant Therapy

18. Intake of medication prohibited due to potential drug-drug interaction (see Section 6.8.2.3, local administration is permitted).

19. Use of other treatments that might interfere with the conduct of the study or the interpretation of the results, including:

    - hormonal medications (see Section 6.8.2.2)
    - other treatments intended for endometriosis/pelvic pain during participation in the study, including the use of herbal products or traditional Chinese medicine for symptom relief, with the exception of the standardized rescue pain medications.

Prior/Concurrent Clinical Study Experience

20. Simultaneous participation in another clinical trial with investigational medicinal product(s). Participation in another trial 3 months prior to Visit 1a that might have an impact on the study objectives, at the discretion of the investigator.

21. Previous assignment to study intervention (randomization) in this study (allowing previously randomized participants to be re-included into the study may lead to bias)

Diagnostic assessments

22. Laboratory values outside the inclusion range (specified in the laboratory manual) and considered clinically relevant[8].

23. Liver safety-related exclusion criteria:

    - ALT above 2 x ULN, OR
    - AST above 2 x ULN, OR
    - Total bilirubin greater than ULN, OR
    - AP above 2 x ULN, OR
    - INR greater than ULN, OR
    - Positive hepatitis B virus surface antigen, OR
    - Positive hepatitis C virus antibodies and detection of mRNA (HCV-mRNA only tested if hepatitis C virus antibodies were detected)

24. Severe hypertension, defined as a sitting systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg

25. eGFR < 30 mL/min/1.73 m^2, calculated by MDRD formula. A different eGFR formula will be used for participants enrolled at sites in Japan in this study (See Section 10.9).

Other Exclusions

26. Wish for pregnancy during the study period

27. Close affiliation with the study site, e.g. a close relative of the investigator, dependent person (e.g. employee or student of the site, or sponsor's staff)

28. Inability to cooperate with the study procedures for any reason, e.g. language comprehension, or inability to get to the study site

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[8] Laboratory tests may be repeated once prior to Visit 1b in case it is medically justified and the investigator expects a non-exclusionary result, with the exception of ALT, AST, AP and hepatitis B and C related tests.

29. Abuse of alcohol or medicines, or use of recreational/illicit drugs, as evaluated by the investigator

30. Otherwise vulnerable patients. Patients who are in custody by order of an authority or a court of law.

5.3 Lifestyle Considerations

Not applicable

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention.

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 (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria and date of last visit.

Re-screening is allowed once only. Re-screening can be performed in the following cases:

- If the inclusion/exclusion criteria preventing participant's initial attempt to participate have been changed via a protocol amendment.
- Screening failures may undergo re-screening within 4 weeks from first screening (counting since Visit 1a) if the eligibility issue that caused the screening failure can be resolved during this period. The 4-week limit is not valid in case inclusion/exclusion criteria have been changed via a protocol amendment
  - Re-screening will not be allowed in participants who failed because of any of the following criteria:
    - inclusion criterion "Type of Participant and Disease Characteristics" number 2
    - inclusion criterion "Type of Participant and Disease Characteristics" number 6
    - exclusion criterion "medical conditions" number 10
    - exclusion criterion "diagnostic assessments" number 23
  - In participants who failed to fulfill exclusion criterion "diagnostic assessments" number 22 it will be decided on a case by case basis whether or not a re-screening is allowed.

The investigator should ensure that the repeated screening procedures do not expose the participant to an unjustifiable health risk.

The participant must sign a new informed consent form for re-screening, even if the content was not changed after the previous consenting. Re-screened participant will be assigned a new participant number.

5.5 Criteria for Temporarily Delaying Enrollment

Not applicable

6. Study Intervention(s) and Concomitant Therapy

Study intervention 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 Intervention(s) Administered

Table 6–1: Study interventions administered

Group Name	BAY 1817080	BAY 1817080 Placebo	Elagolix
Intervention Name	BAY 1817080	placebo for BAY 1817080	elagolix
Type	drug	placebo	drug
Dose Formulation	tablet	tablet	tablet
Unit Dose Strength(s)	25 mg and 100 mg	N/A	150 mg
Dosage Level(s)	25 mg, 75 mg and 150 mg BID	N/A	150 mg QD
Route of Administration	oral	oral	oral
Use	experimental	placebo	active comparator
Packaging and Labeling	Study Intervention will be provided in blisters. Study Intervention will be labeled as required per country requirement	Study Intervention will be provided in blisters. Study Intervention will be labeled as required per country requirement	Study Intervention will be provided in blisters. Study Intervention will be labeled as required per country requirement
[Current/Former Name(s) or Alias(es)]	N/A	N/A	Orilissa ®

- Participants will take study intervention:
  - BAY 1817080 or matching placebo twice daily (morning and evening doses) at approximately the same time each day 12 hours apart, OR
  - Elagolix once daily at approximately the same time each day 24 hours apart.
  - To the effect that they will receive (according to assigned treatment groups):
    - Treatment group 1: 2 tablets of 25 mg BAY 1817080, 1 tablet of 100mg BAY 1817080 and one tablet of 25 mg placebo to BAY 1817080
    - Treatment group 2: 3 tablets of 25 mg BAY 1817080 and one tablet of 100mg placebo to BAY 1817080

- Treatment group 3: 1 tablet of 25mg BAY 1817080, 2 tablets of 25mg placebo to BAY 1817080 and one tablet of 100mg placebo to BAY 1817080
- Treatment group 4: 3 tablets of placebo for 25mg, and 1 tablet of placebo for 100mg placebo to BAY 1817080
- Treatment group 5: One tablet of elagolix 150mg

For Treatment groups 1-4 participants will receive Placebo for BAY 1817080 due to blinding reasons. Participants are recommended to take the tablets at approximately the same time each day with or without food.

- Participants from China and Japan will only be randomized to treatment groups 1 to 4.
- Study interventions are not to be broken, halved or crushed; they should be swallowed as a complete unit with water.
- Study intervention can be taken with food or without food. See Section 8.4 for detailed instructions regarding recording of the drug intake and the food intake before or after the drug intake in relation to blood sampling for PK.
- If a dose of study intervention has been missed:
  - Treatment groups 1-4:
    - If ≤ 6 hours has passed since the dose was due, it should be taken immediately
    - If > 6 hours have passed since the dose was due, the dose should be skipped and the next dose should be taken according to the regular schedule.
  - Treatment group 5:
    Instruct the participant to take the missed dose on the same day as soon as she remembers and then resume the regular dosing schedule. Not more than 1 tablet should be taken each day.

6.2 Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm that study interventions have been received and appropriate temperature conditions, if applicable, have been maintained during transit. Any discrepancies are to be reported and resolved before use of the study intervention.
2. Only participants assigned to treatment in the study may receive study intervention, and only authorized site personnel or delegates may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator or the head of the institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Study intervention returns, reconciliation and removal for destruction information will be captured in IWRS.

4. Further guidance and information for the final disposition of unused study interventions are provided in Investigator Site File.
5. Study intervention may only be dispensed to a study participant after ruling out pregnancy (urine pregnancy test with negative result).

6.3 Measures to Minimize Bias: Randomization and Blinding

- Participants who meet all eligibility criteria will be centrally randomized by assigning a unique randomization number on Visit 1b using an IWRS system.
- Once a randomization number has been assigned it must not be re-assigned.
- The randomization number encodes the participant's assignment to one of the five treatment groups of the study, according to the randomization plan.
- Randomization plan is a computer-generated list produced prior to the study start by the sponsor or delegate, and provided to the IWRS provider. Scrambled randomization plan will be used in this study.
- Site personnel will be trained for the use of the IWRS during the Investigator's Training and/or during the Site Initiation. The instructions for the use of the IWRS will be provided in the Investigator Site File.
- Double-blinded and open-label study intervention will be dispensed to all randomized participants according to the instructions by the IWRS as summarized in the SoA.
- Returned study interventions may not be re-dispensed
- The blinding will be maintained by the following measures:
    - Tablets containing 25 mg of BAY 1817080 and corresponding placebo are identical in appearance (size, color, shape)
    - Tablets containing 100 mg of BAY 1817080 and corresponding placebo are identical in appearance (size, color, shape)
    - The route of administration, will be the same for all participants within Japan and China and the rest of the world, respectively.
    - The study intervention packages will be labeled with a unique number, and assigned to a participant through the IWRS
    - The randomization number will be unavailable for either the site personnel or the study team until unblinding.

Unblinding

- Unblinding during the study conduct can be done using the IWRS, according to the blind-breaking instructions.
- The investigator has the responsibility for determining if unblinding of a participant's study intervention assignment is warranted when knowledge of the actual treatment is absolutely essential for further medical management of the participant. Participant's safety must always be the first consideration in making such a determination.

- If the investigator decides that unblinding is warranted, the investigator should contact the sponsor prior to unblinding unless this could delay emergency treatment of the participant.
- If the investigator is unavailable, and a treating physician not associated with the study requests emergency unblinding, the emergency unblinding requests are forwarded to the emergency medical advice service that is available 24 hours/7 days (applying the same criteria for unblinding as described above, country-specific emergency contact information provided in the participant card).
- If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason for unblinding must be recorded in the source documentation and the eCRF.
- For regulatory reporting purposes, sponsor's Global Pharmacovigilance is permitted to unblind individual cases.
- In compliance with applicable regulations, in the event of a SUSAR, the participant's intervention is unblinded before reporting to the health authorities and IECs.
- Participants who are unblinded to the study team and/or to the investigators may be withdrawn from the study intervention.
- Sponsor's bioanalytical, pharmacometrics and pharmacokinetics personnel will be unblinded prior to the database lock, and/or interims analyses according to the corresponding sponsor's Standard Operating Procedures. Appropriate measures are taken to maintain blinding of the study team, e.g. data will be stored separately, and members of the study team will neither have access to the randomization list nor to individual data.

6.4 Study Intervention Compliance

- Participant compliance with use of study drug intervention will be assessed based on accountability:
    - Study intervention will be dispensed according to the SoA.
    - Participants are asked to return all unused study interventions and empty packages to the study site according to the SoA for accountability purposes.
    - Compliance will be assessed by direct questioning, and counting the number of returned tablets (recordings in the eDiary will not be used as a source).
    - Investigator or delegate is requested to document all dispensed and returned study intervention per study participant.
    - Any discrepancy between expected and actual number of tablets used/returned should be discussed with the study participant. Deviation(s) from the prescribed dosage regimen should be recorded.
- Concentration of the study intervention will be measured from the participant's PK samples as summarized in the SoA.
- Special attention should be paid to follow compliance at the beginning of intervention to ensure correct understanding of the instructions.

6.5 Dose Modification

Not applicable in this study.

6.6 Continued access to Study Intervention after the End of the Study

- Study participants will not be given further access to the study intervention (BAY 1817080 or the active comparator).
- After end of the study, participants will receive routine medical care based on local medical practice. No restrictions regarding the choice of medical care apply after completion of the study.

6.7 Treatment of Overdose

In this study, an overdose is defined as an intentional or accidental administration of investigational drug, to or by a study participant, at a dose which is higher than the dose assigned to that individual participant according to the study protocol.

There is no known specific treatment (no antidote) for an overdose with BAY 1817080 or elagolix. An overdose should be treated as clinically indicated based on signs and symptoms.

Overdose *per se* will not be reported as an AE and/or SAE unless it is associated with clinically relevant signs and/or symptoms, or an intentional overdose taken with possible suicidal and/or self-harming intent (see Sections 10.3.1 and 10.3.2).

In the event of an overdose, the investigator should:

- Contact the Sponsor as soon as possible.
- Evaluate the participant to determine, in consultation with the Sponsor, if needed, whether study intervention should be interrupted.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 14 days.
- Document the quantity of the excess dose as well as the duration of the overdose.

Decisions regarding dose interruptions will be made by the investigator in consultation with the Sponsor, if needed, based on the clinical evaluation of the participant.

6.8 Concomitant Therapy

Any medications (including over-the-counter or prescription medicines, contrast media, vaccines), vitamins and/or herbal supplements that the participant uses during the study participation must be recorded along with:

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

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

6.8.1 Standardized Rescue Pain Medication

Participants will be instructed to use standardized rescue medication only when relief of pelvic pain currently being experienced is required, i.e. not prophylactically.

Standardized rescue pain medication for endometriosis-associated pain will be prescribed for participants by the investigator and limited to ibuprofen tablets (containing 200mg or 400 mg ibuprofen per tablet, depending on local country regulations). In addition to ibuprofen, alternatively acetaminophen/paracetamol 500 mg and/or Tramadol 50 mg *may* be prescribed to participants who do not obtain sufficient relief from the study intervention and ibuprofen.

The standardized rescue medication is considered an authorized auxiliary medicinal product (not an investigational medicinal product). The maximal single and daily dose and dosing interval should be approved by the investigator and be in line with the product prescribing information for that particular dosage form in that country.

Investigators will prescribe these standardized rescue pain medications for participants at the time of entry into the screening phase, taking into consideration their preference and/or historical use of analgesics. The same rescue pain medication (type and dose preparation) used during the screening phase should be used as needed for rescue during the entire study. Participants will be instructed to contact the site if an escalation (in dose, frequency or category) in their analgesic medication from what was last prescribed by the investigator is needed, so that appropriate adjustments can be made. Participants will be instructed not to increase their total daily dose or frequency of rescue pain medication or to escalate the category of analgesic used (i.e., from ibuprofen or acetaminophen to a narcotic containing medication) unless it is necessary, after a discussion between the participant and the investigator.

Daily use of standardized rescue pain medication will be recorded by the participant in the hand-held device during the entire study. This will include specific dosing information of the permitted rescue pain medication, including dose and total number of pills/tablets within a 24-hour period and the information whether it was taken for pain in the target area or not. Local pharmacy or sites have responsibility for documentation e.g., in case of recall according to their local requirements.

If the rescue pain medication is used for pain related to other conditions (e.g. headache, joint pain), these conditions must be recorded as AEs, and the pain medication used for their treatment documented as concomitant medication in the corresponding eCRFs.

6.8.2 Prohibited Medications

6.8.2.1 Pain Medication other than permitted standardized rescue medication

- Use of all other analgesics beyond the permitted rescue pain medication is discouraged during the study since it potentially disturbs the study outcome
- If any other pain medication is taken, for any reason (including EAPP), it must be recorded in the eCRF

6.8.2.2 Hormonal Medications

- Hormonal medications listed in Table 6–2 are prohibited during participation in this study
- Participants using hormonal treatment at Visit 1a must be willing to stop this at the next suitable time point at or following Visit 1a as outlined in Table 6–2

Table 6–2: Discontinuation of Hormonal Medications

Hormonal medications before the study	Timing of stopping hormonal medications	Bleeding which counts as the 1st menstrual bleeding after Visit 1a
Cyclic combined contraceptives (oral, vaginal, or transdermal)	Complete the current cycle ongoing at Visit 1a	Withdrawal bleeding which occurs at the end of the cycle ongoing at Visit 1a
Short-acting progestins or extended regimen of COC	Stop at Visit 1a	Withdrawal bleeding after stopping treatment
Hormone-releasing IUDs (Jaydess™, Kyleena™, Liletta™ and Mirena™) or subdermal implants	Not allowed during the study, users are only eligible if IUD/implant was coincidentally removed shortly before Visit 1a and normal menses have resumed before Visit 1a, and participant is willing to defer restart of IUD/implant use until after study participation. Removal of the IUD/implant for study participation only is not allowed.	First menstrual bleeding after Visit 1a (as participants entering the study without hormonal treatment)
GnRH-agonists or long-acting hormonal contraceptive (injectables)	Not allowed during the study, users are only eligible if the last injection was administered more than one application interval before Visit 1a and normal menses have resumed before Visit 1a.	First menstrual bleeding after Visit 1a (as participants entering the study without hormonal treatment)
GnRH-antagonists and progesterone receptor modulators	Not allowed during the study, users are only eligible if it has been stopped at least 28 days before Visit 1a and normal menses have resumed before Visit 1a	First menstrual bleeding after Visit 1a (as participants entering the study without hormonal treatment)
Hormonal replacement treatments (e.g. add-back therapy for menopausal symptoms from GnRH-analogues)	Not allowed during the study, users are only eligible if it has been stopped before Visit 1a and normal menses have resumed before Visit 1a	First menstrual bleeding after Visit 1a (as participants entering the study without hormonal treatment)

COC = combined oral contraceptive, IUD = intrauterine device, GnRH-a = Gonadotropin-releasing hormone agonists

6.8.2.3 Medication Prohibited Due to Potential Drug-Drug Interaction

Strong CYP3A4 inducers and strong CYP3A4 inhibitors

The following strong CYP3A4 inducers and strong CYP3A4 inhibitors are prohibited within the last 4 weeks before start of study intervention and during the intervention period of this study:

- **CYP3A4 inducers:** e.g. St. John's wort, rifampicin, carbamazepine, phenytoin
- **CYP3A4 inhibitors**: e.g. itraconazole, posaconazole, voriconazole, ritonavir, nelfinavir or other inhibitors of human immunodeficiency virus protease, clarithromycin, telithromycin, nefazodone, telaprevir, boceprevir

For examples of common inducers and inhibitors of CYP3A4 see Section 10.7.

Note: ketoconazole and other triazole antifungal drugs are allowed for topical/local use (including vaginal application).

Strong OATP1B1 inhibitors

- Strong organic anion transporting polypeptide (OATP) 1B1 inhibitors (e.g., cyclosporine and gemfibrozil) during the intervention period of this study.

OATP1B1/1B3, BCRP and P-gp substrates

Based on preclinical data, an increase in exposure of OATP1B1/1B3, P-gp and BCRP substrates during co-administration of BAY 1817080 due to inhibition of those transporters by BAY 1817080 cannot be excluded.

- Apixaban, dabigatran, edoxaban, digoxin: prohibited within the last 2 weeks prior to start of treatment and until 2 weeks after end of intervention period of this study.
- Participants receiving a combination of BAY 1817080 and OATP1B1/1B3, BCRP and P-gp substrates should be closely monitored for signs and symptoms of adverse events due to increased exposure of co-administered OATP1B1/1B3, BCRP and P-gp substrates.
- Dose modification of OATP1B1/1B3, BCRP and P-gp substrates should be considered based on the prescriber information or such compounds should be avoided. Typical OATP1B1, OATP1B3, BCRP and P-gp substrates include but are not limited to the following: fexofenadine, sulfasalazine, rosuvastatin, atorvastatin, cerivastatin, glyburide, pravastatin, repaglinide, simvastatin.

A clinical DDI study investigating the effect of BAY 1817080 on the sensitive OATP1B1/1B3 and BCRP substrate rosuvastatin is ongoing.

Please refer to the current version of the IB for further information.

Additional information can be found in Table 5-1 of the FDA DDI guidance (19).

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study, receive the procedures scheduled for the end of intervention visit (i.e. visit 5) as soon as possible, and then be evaluated for the whole follow-up phase. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

- Participants must discontinue study intervention if any of the following occurs:
  - In the investigator's opinion, continuation of the study intervention would be harmful to the participant's well-being
  - Surgical treatment of endometriosis[9]
  - Liver safety-related discontinuation criteria are met (see Section 10.6)
  - Pregnancy (see Sections 8.3.5 and 10.4)
  - At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns)
- Participants may be withdrawn from study intervention if any of the inclusion criteria are no longer fulfilled or if any of the exclusion criteria apply during treatment.

7.1.1 Rechallenge

Study intervention may be restarted after a temporary interruption if deemed clinically appropriate by the investigator in collaboration with the Bayer Medical Monitor.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or compliance reasons. This is expected to be uncommon.
  - If a participant becomes SARS-CoV-2 virus RNA test positive while on study, the investigator will have to decide whether staying in the study is compatible with participant and site personnel safety and wellbeing. The decision should also take into account possible interaction between the test drug and potential antiviral medication.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

[9] If possible, Visit 5 should be performed as close to the timeframe in the SoA as possible but before surgery

  - Participants who have been randomized but not yet started study intervention do not need to undergo further study procedures other than return of supplies, before their study participation terminates.
  - For withdrawal during the intervention phase, the participant should undergo assessments scheduled for the end of intervention visit (Visit 5) plus physical examination and return of supplies
  - For withdrawal during the follow-up period, the participant should undergo the assessments scheduled for the next visit (Visit 6 or 7)

- The participant will be permanently discontinued both from the study intervention and from the study at that 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.

A participant is called “dropout” if she was randomized and discontinues study participation prematurely for any reason.

7.3 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 clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not 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.
- If the participant is reached, the site personnel must:
  - Ascertain whether or not the participant wishes to continue in the study
  - Counsel the participant on the importance of maintaining the assigned visit schedule and
  - Reschedule the missed visit as soon as possible
  - In case study intervention was interrupted, the investigator should check whether permanent withdrawal from study intervention was required (see Section 7.1)

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. 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 intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet 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.
- MRI, ultrasound (in Japan only) and cervical smear conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures were performed within the time frame defined in Section 5.1 (inclusion criteria #2 and #7).
- Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed approximately 350 mL
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

Planned time points for all efficacy and immunogenicity assessments are provided in the SoA.

8.1.1 Patient-Reported Outcomes (PROs)

- PROs will be responded to by the study participants themselves without any assistance.
- PROs will be collected using an electronic handheld diary (eDiary) except for the PCS and painDETECT, which are collected as paper questionnaires. Paper questionnaires will not be used as replacement for the eDiary device.
- Site personnel as well as study participants will receive validated training (20, 21) to ascertain accurate and reliable reporting of pain scores, proper use of pain scales and minimization of placebo response. Training will be provided at study start and retraining will be performed at regular intervals and as needed during the course of the trial.

- Site personnel will be trained for the PROs, use of eDiary device and related internet portal (used for review of data) during the Investigator's Training and/or during the Site Initiation. The paper PROs, instructions for the use of the eDiary and portal will be provided in the Investigator Site File.
- Site personnel will provide technical guidance for the study participants. In addition, a 24-hour help desk in local languages will be available. No other help than technical support will be given to study participants regarding the completion of the PROs. Study participants will be asked to confirm their understanding on the use of the eDiary device and completion of the questionnaires.
- When study participants complete PROs at the site, they should do so before other study procedures. The questionnaires should be completed independently by the participant herself in a quiet, private area. The site should allocate adequate time for completion of all PROs at respective visits.
- At no time is the site personnel allowed to respond to other than technical questions.
- The site personnel should check the ePRO entries via the internet portal/reports.
- Allowed ePRO data changes are described in the Vendor documentation.

8.1.1.1 Endometriosis Symptom Diary (ESD)

- The ESD v 9.0 is a multi-item PRO instrument designed to assess the patient's experience of endometriosis symptoms.
- Item 1 of the ESD serves as the primary endpoint in this study.
- This PRO was first used in a validation study (22) and subsequently in a treatment study with an aromatase inhibitor (23). Regarding the rationale for developing the ESD, see Gerlinger et al. 2012 (24). In order to evaluate psychometric properties, ESD pain items will be complemented by pain recordings using 4-week recall VAS.
- The ESD will be completed by the study participant each evening (between 18:00 and 24:00 preferably after intake of the evening dose), when she is to reflect on her experiences during the past 24 hours.
- Participants will be asked to record their:
    - endometriosis pain at its worst (single items 1-3)
    - vaginal bleeding (single item 4)
    - sexual intercourse and dyspareunia (single items 5-7)
    - use of study intervention (single item 8)
    - use of standardized rescue medication and other pain medication (single items 9-11).
- Single items rating symptoms (1, 2, 3, and 6) are reported using a 0 to 10 NRS.

- Items concerning having or avoiding sexual intercourse (5 and 7) and intake of pain medications (9, and 10) use a dichotomous yes/no scoring system (in addition, the number of each of the pain medications taken will also be recorded). The item for study intervention (8) quantifies the number of tablets taken.
- Vaginal bleeding intensity (item 4) will be assessed; the response that best describes the vaginal bleeding during the past 24 hours is to be selected on a categorical response scale (5 levels of increasing intensity: none, spotting, light, normal, heavy).

8.1.1.2 Endometriosis Impact Scale (EIS)

- EIS version 5.0 is a multi-item PRO instrument designed to assess the impact of endometriosis symptoms on the patients' lives.
- EIS was used in a validation study (22) and subsequently in a treatment study with an aromatase inhibitor (17). Regarding the rationale of developing the EIS, see Gerlinger et al. 2012 (24).
- The EIS will be completed by the study participant once a week (between 18:00 and 24:00), when she is to reflect on her experiences during the past 7 days. In case a study participant misses to enter data, EIS will be available for data entry the next day.
- Participants are to reflect on the effect of endometriosis pain on their daily lives during the past 7 days. Participants will be asked to describe impacts on:
    - physical activities (physical subscale; contains 7 single items)
    - emotional effect (emotional subscale; contains 7 single items)
    - sexual activities (sexual activities subscale; contains 3 single items)
    - ability to concentrate
    - ability to sleep
    - household activities
    - paid work or study
    - social and leisure activities
- Participants will be asked to rate on a 5- to 6-point scale (6-point scales are used for items which allow for the rating of a "does not apply" option) where 0 represents "does not apply", 1 represents "not at all" and 5 represents "extremely".

8.1.1.3 Visual Analogue Scale (VAS) for Pelvic Pain

- VAS is commonly used for the assessment of pain in various indications. It has been used for development of Visanne (dienogest) in endometriosis and hence allows for comparison with historical data (25).
- VAS consists of a straight line offering 101 positions/dots to choose from, with verbal anchors at either end, representing a continuum of pain intensity. One end of the line has the anchor "no pain" while the other end of the line has the anchor "unbearable pain".
- Study participants will be asked to indicate their level of pelvic pain over the last 4 weeks with a single vertical mark on the line. Pelvic pain refers to endometriosis pain in the lower abdomen and surrounding areas.

- VAS will be completed during the site visits in the eDiary.

8.1.1.4 Patient Global Impression of Severity (PGI-S) and Change (PGI-C)

- PGI-S and PGI-C are self-administered instruments used in former endometriosis trials. Inclusion into this study will contribute to the investigation of psychometric properties of ESD and EIS.
- PGI-S asks the participant to rate severity of the endometriosis pain over past 4 weeks using a 6-point verbal single-item rating Likert scale (no pain, very mild, mild, moderate, severe, and very severe).
- PGI-C measures change in the participants' endometriosis pain since the start of the study intervention on a single-item 5-point Likert scale ranging from "much better" to "much worse".
- PGI-S and PGI-C will be completed during the site visits in eDiary.

8.1.1.5 PainDETECT

- The painDETECT PRO was developed and its properties were originally tested on a sample of lower-back pain patients; additional PRO and clinical research is summarized by Freynhagen et al. (26). There is limited evidence for applicability and validity of painDETECT in endometriosis, hence it will be used and data evaluated as an explorative endpoint.
- PainDETECT data will be collected on paper questionnaire in this study to explore and describe potential presence of neuropathic pain and the change under intervention.
- The painDETECT is a self-administered 13-item paper questionnaire to screen the patients with neuropathic pain (26). It includes 3 domains:
    - pain course pattern
    - pain radiation
    - sensory symptoms.
- A painDETECT score is generated for each participant by assigning a value to items 7–13 (0 = "never" to 5 = "very strongly") and summating the result. This score is then adjusted, based on responses to items about pain course pattern and pain radiation.
- The final score range is from -1 to 38. For screening purposes, the below cut-off points have been suggested in other indications and will be used in this study exploratively, as there is limited evidence on using painDETECT and validity of these thresholds for endometriosis indication.
    - score $\leq$ 12, a neuropathic component is unlikely (< 15%)
    - score $\geq$ 19, a neuropathic component is likely (> 90%)
    - Between these, the result is uncertain, i.e. a neuropathic pain component can be present.

8.1.1.6 EuroQoL 5-dimension 5-level (EQ-5D-5L)

The EQ-5D-5L is a self-administered preference-based generic measure of health status which includes five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (27). Patients provide a rating for each question on a five-level Likert scale: having no problems, having slight problems, having moderate problems, having severe problems and being unable to do/having extreme problems. In addition, patients are asked to self-rate their own health today on a vertical 0-100 unit visual analogue scale (VAS), with 0 corresponding to "the worst health you can imagine", and 100 corresponding to "the best health you can imagine".

EQ-5D-5L will be collected on eDiary and programmed after EIS data collection weekly during screening phase before treatment and monthly (every 4 weeks) during the treatment phase and follow up.

The reported data will be analyzed descriptively. The utility analyses based on collected EQ-5D-5L data are planned to be conducted in separate post-hoc analyses.

8.1.1.7 Modified Work Productivity and Activity Impairment questionnaire (mWPAI)

Work Productivity and Activity Impairment Questionnaire is commonly used to assess the impact of different health conditions including gynecological indications on absenteeism, presenteeism and activity impairment (28). Modified version for Endometriosis (mWPAI) with 6 items with recall over past 4 weeks will be used. The items will be analyzed descriptively, there is no total score. The data will be collected on eDiary during the site visits as indicated in the SoA (29, 30).

8.1.1.8 Pain Catastrophizing Scale (PCS)

The Pain Catastrophizing Scale (PCS) is a 13-item instrument derived from concepts of catastrophizing described in the literature (Chaves & Brown, 1987; Spanos et al., 1979) as well as items from the catastrophizing subscale of the Coping Strategy Questionnaire (31).

The PCS instructions ask patients to reflect on past painful experiences, and to indicate the degree to which they experienced each of 13 thoughts or feelings when experiencing pain, on 5-point scales with the end points (0) not at all and (4) all the time. The PCS yields a total score and three subscale scores assessing rumination, magnification and helplessness. The total score is computed by summing responses to all 13 items. PCS total scores range from 0 – 52 (32).

The PCS data will be collected on paper at baseline as an explorative endpoint to better understand pain-related distress experienced by women with endometriosis. The results will be reported descriptively without applying any cut-off points or thresholds.

8.1.1.9 Additional daily symptom items

Three additional items will be asked and reported daily by patient on eDiary to assess dyschezia (pain associated with bowel movement), dysuria (pain associated with urination) and number of hot flushes. These questions will be completed by the study participant each evening (between 18:00 and 24:00) together with the ESD.

The patients will be asked to report pain at its worst during the past 24 hours on 0-10 NRS scale to assess dyschezia and dysuria. These items were derived from previous qualitative research and development of ESD.

In addition, the number of hot flushes (sensation of heat with sweating) in the past 24 hours will be reported to assess tolerability of different active treatments.

8.2 Safety Assessments

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

8.2.1 Physical and Gynecological Examinations

- Physical examination includes, at a minimum, assessments of the skin, the lungs, cardiovascular system and abdomen (liver and spleen).
- Gynecological examination is to be done according to local guidelines/common clinical practice.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- In the event of any suspicious finding during examinations, further diagnostic investigations should be performed at the discretion of the investigator.
- Abnormal examination findings are to be recorded either as medical history or as AEs (see Section 8.3.1).

Height and weight will be measured and recorded. For weight measurement the participant may wear indoor clothing with no shoes. The clothing should be alike at all measurements.

8.2.2 Vital Signs

Blood pressure and heart rate will be assessed. Measurements should be:

- Preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions
- Assessed in a sitting position
- 1 heart rate and 1 blood pressure reading. The readings will be recorded in the eCRF, as well as corresponding AEs or medical history, if clinically relevant.

8.2.3 Ultrasound

- Ultrasound examination should be performed by a physician well experienced in gynecology or with corresponding qualification based on local clinical practice
- Preferably the evaluation should be performed by transvaginal ultrasound. However, if deemed appropriate, transabdominal or transrectal ultrasound examinations can be performed in addition or instead. The chosen method (s) should be used consistently throughout the study.

- The following safety parameters will be measured and recorded:
  - Endometrial thickness (measured in the medio-sagittal section as double-layer in millimeters)
  - Evaluation of the ovaries
  - Endometriosis
  - Adenomyosis
  - Any other pathology detected during the examination
- In case of any suspicious finding, further diagnostic investigations should be performed at the discretion of the investigator.
- The minimum documentation will include printouts and/or CDs with images from the ultrasound machine showing the endometrium in sagittal section and both ovaries. The printouts and/or CDs with images have to be labeled unambiguously, containing at least the study number, participant number, time point, endometrial thickness, and laterality (left/right) for ovaries. If the printouts are on thermo-sensitive paper, they need to be copied as they will fade over time.

8.2.4 Cervical cytology

- Cervical smear should be obtained at Visit 1a or shortly after Visit 1a.
- Cervical smear performed during the last 12 months prior to Visit 1a can be used for the screening assessment.
- Participants with ASCUS are eligible for the study if they have negative result for high-risk HPV strains from an HPV deoxyribonucleic acid test.
- Cervical smear can be repeated once in case of insufficient material in the sample.
- Cervical smear will only be performed before randomization to ensure eligibility and is not a safety endpoint.

8.2.5 Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
  - All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
  - If laboratory values from non-protocol specified laboratory tests performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded.

- Laboratory tests may be repeated once prior to Visit 1b in case it is medically justified, and the investigator expects a non-exclusionary result, with the exception of ALT, AST, AP and hepatitis B and C related tests
- For information regarding laboratory assessments related to liver safety, see Section 10.6.

8.2.6 Pregnancy Testing

All participants of the study are women of childbearing potential, thus should receive pregnancy tests according to the SoA. Additionally, the participant is asked to conduct home urine pregnancy testing whenever there is suspicion of a pregnancy (See Section 10.4)

8.2.7 Suicidal Ideation and Behavior Risk Monitoring

Suicidal ideation and behavior have been reported in patients treated with the active comparator (elagolix) (please see section 2.3.1). Therefore, after the start of study intervention, participants should be

- Monitored for new or worsening depression, anxiety or other mood changes, as well as any unusual changes in behavior. Participants with such signs should be referred to a mental health professional, as appropriate.
- Advised to seek immediate medical attention for suicidal ideation or behavior.
- Put through a risk assessment where all possible factors contributing to suicidal ideation and behavior are evaluated and discontinuation of the study intervention is considered.

8.3 Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

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

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

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

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the follow-up visit, i.e., Visit 6 or 7, respectively, at the time points specified in the SoA (Section 1.3).

Additional details on smell and taste related AEs will be collected once at the end of an individual’s study participation via dedicated eCRF pages.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of learning of the event, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not 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 discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

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

8.3.3 Follow-up of AEs and SAEs

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

8.3.4 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 intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ IECs, and investigators.
- For all studies except those utilizing medical devices investigator safety reports must be prepared for SUSAR according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

- Details of all pregnancies will be collected after the start of study intervention and until the end of study. Time period for reporting pregnancies should align with the time period for post-intervention contraception determined in Section 5.1.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs, and will be reported as such.
- 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.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any participant who becomes pregnant while participating in the study will discontinue study intervention.

8.3.6 Taste Related AEs

- Taste-related AEs will be recorded if reported by the participant
- At the EoT visit, there will be additional questions posed to those participants who spontaneously reported a taste-related AE which occurred during the intervention period:
    - Question for frequency
    - Question on how bothersome the taste effect was
- Additional details on smell and taste related AEs will be collected once at the end of an individual's study participation via dedicated eCRF pages.

8.3.7 Adverse Events of Special Interest

Adverse events of special interest have to be reported to the sponsor along the timelines set for SAEs, i.e. within 24 hours of the investigator's awareness, as described in Section 8.3.1.

Declaration of an event as serious should only occur if one or more of the serious criteria is applicable. Non-serious adverse events of special interest should not automatically be upgraded to serious by the reporting investigator.

Adverse events of special interest are liver enzyme increases meeting the following criteria:

- ALT and/or AST >8x ULN OR
- ALT and/or AST >3x ULN with total bilirubin >2x ULN.

8.4 Pharmacokinetics

- PK samples will be collected from participants in treatment groups 1-4 to maintain blinding; however, PK samples from the placebo treatment group will not be analyzed (placebo samples might be analyzed e.g. in case of suspected treatment errors).

- Sparse blood PK samples will be collected for measurement of plasma concentrations of BAY 1817080 as specified in the SoA:
  - Pre-dose sample will be taken at Visits 2, 3 and 5, at least 10 hours after the previous dose (NA for Visit 2). Study intervention will be administered at the study site after the pre-dose sample at these visits. The following must be recorded:
    - Time of the last dose taken at home before the site visit
    - Time of the closest food intake before or after that last dose taken at home
    - Time of the closest food intake before or during dose taken at the site.
  - Two post-dose samples will be taken at Visit 2 and 5: first sample 2 (±1) hours and the second sample 4 (±1) hours after the first daily dose, with at least 1 hour between. Time of the closest food intake before or after the dose must be recorded.
  - One post-dose sample will be taken at Visit 4, at least 5 hours after the previous dose taken at home. The following must be recorded:
    - Time of the previous dose taken at home before the site visit
    - Time of the closest food intake before or after that first dose taken at home
- It is of importance that the actual date and time (24-hour clock time) of blood sampling are documented in the eCRF because PK calculations will be based on the actual sampling times relative to dosing times.
- A maximum of 2 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling, may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Plasma concentrations of BAY 1817080 from sparse PK sampling will be determined using validated analytical methods.
- Samples will be used to evaluate the PK of BAY 1817080 as an exploratory endpoint in this study.

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

Detailed instructions about the collection, processing, storage and shipment of biological samples will be provided separately (e.g. sample handling sheets or laboratory manual).

Population pharmacokinetic (popPK) analysis

The systemic exposure of BAY 1817080, drug-related PD biomarker and/or safety and efficacy measurements collected during the trial might be analyzed using nonlinear mixed effects modeling.

Mixed effects models, e.g., popPK models, describe the relationship between dose and time and variables such as drug plasma concentrations. Both structural and random effects are involved in this relationship. A preliminary popPK compartmental model will be further developed using the concentration of the drug as the dependent variable.

The potential influence of relevant participant covariates (e.g., body weight) and optionally efficacy, PD biomarkers or safety laboratory parameter can be included in the PK/PD modeling using population approaches. A separate evaluation plan, providing details of the model building process and evaluation will be provided prior to the beginning of the popPK/PD analysis. Results obtained by popPK/PD modeling will be presented in a separate report that may also include PK data from other studies with BAY 1817080 or published PK data on elagolix.

The modeling analyses may be started prior to database lock. If this is applicable, appropriate measures will be taken to maintain blinding of the study team, e.g., data will be stored separately, and members of the study team will neither have access to the randomization list nor to individual data.

Plasma concentration data for all participants will be listed in the clinical study report.

Pharmacodynamic parameters are not evaluated in this study.

8.5 Genetics

Genetic as well as non-genetic analyses may be part of the biomarker investigations in this study if approved by local IECs / IRBs and competent authorities, in all countries except for China. Genetic investigations may be of any kind, except for the whole genome sequencing.

A sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study. Details on sample handling will be provided separately. See Section 8.6 for details.

8.6 Biomarkers

In this study, genetic as well as non-genetic biomarkers will be investigated in participants from all countries except for China.

- **Timing** – see SoA for planned time points of sample collection.
- **Sample handling and storage** – details on the collection, processing, shipment and storage of samples will be provided in separate documents (e.g. sample handling sheets or lab manual). Samples may be stored for a maximum of 15 years (or according to local regulations) following the end of the study at a facility selected by the sponsor to enable further analyses.
- **Medical history information** – if any additional information about the status of disease was collected in the course of treatment prior to entry of the participant in the study, the results may be collected in order to include this data in biomarker analyses.
- **Reporting** – the results of biomarker investigations may be reported separately (e.g. in a biomarker evaluation report).

8.6.1 Biomarkers Monitoring Disease Activity

Serum and plasma will be investigated for e.g. interleukins, high sensitivity C-reactive protein, and neurotrophins:

- Endometriosis is an inflammatory condition with significantly altered local cytokine and neurotrophin milieu in the peritoneal cavity

- Concentrations of selected immune- and neurotrophin related BMs have been described as being altered not only locally but also systemically in serum/plasma
- Serum concentrations of CA125, CA19-9 and B2M will be investigated within lab parameters to evaluate their diagnostic and monitoring value in endometriosis patients (see Section 10.2).

Analysis of key steroids (estrogen and progesterone) may be conducted in BM samples and utilized for the analysis of disease activity BMs:

- Many inflammatory BMs undergo cyclical modulation during the menstrual cycle, resulting data will need to be investigated in a cycle-controlled manner
- Study visits are scheduled to reflect the intervention period and do not reflect individual cycle lengths and characteristics

8.6.2 Biomarkers Related to Ovarian Activity

Regular menstrual cycles are considered relevant indicators of reproductive health in women and changes may impact the quality of life. In order to demonstrate that BAY 1817080 has no effect on the menstrual cycle and ovarian activity, parameters indicative of ovarian activity will be assessed in this study.

Following parameters will be taken into account to assess ovarian activity:

- Regular menstrual bleeding
- Serum progesterone >3 ng/mL

8.6.2.1 Bleeding Pattern

- Menstrual bleeding pattern can be seen as a noninvasive marker for endocrine status in the studied cycle (33).
- The information on menstrual bleeding will be derived from Item 4 in the ESD (see Section 8.1.1.1).
- Cycle length and bleeding duration as well as an average intensity will be calculated.

8.6.2.2 Diameter of Ovarian Follicles

- Throughout the cycle, the diameter of the largest healthy follicles, with the exception of the dominant follicle, does not exceed on average 6 mm during the follicular phase and 4 mm during the luteal phase. The dominant follicle has a linear daily diameter growth of 2–3 mm per day, and at the moment of ovulation, the diameter of the dominant follicle is 18–27 mm.
- During the ultrasound examination (see Section 8.2.1), ovarian follicles should be monitored. The size of the largest follicle (if mean diameter > 10 mm) as well as presence of a ruptured follicle or corpus luteum should be recorded in the eCRF.
- Follicles larger than 18 mm, ruptured follicles, as well as structures identified as corpus luteum will be indicative of an ovulatory cycle.

8.6.2.3 Serum Progesterone

Serum progesterone will be investigated from blood samples at each visit. Progesterone level ≥ 3 ng/mL (9.5 nmol/L) will be considered indicative of a recent ovulation (33, 34).

8.6.3 Sleep Quality and Activity Measurement

Investigation of sleep quality and activity is considered as an option for an additional, objectively assessed, marker demonstrating improvement of patient outcome; further, the degree of baseline sleep disturbance could predict the response to treatment.

Optional participation in a sleep quality and activity substudy will be offered to a subset of participants. This will be limited to certain countries at the sponsor's discretion.

In an exploratory biomarker analysis, different parameters characterizing sleep quality (e.g. total sleep time, sleep onset latency, sleep efficiency) and daily activity (e.g. number of steps taken, physical activity intensity, sedentary bouts) will be investigated retrospectively (see Section 10.8 for details).

In addition to the objective sleep monitoring by wearable, all participants will be provided a sleep questionnaire developed to assess pain associated sleep disturbance (for time points, refer to SoA).

Pain and Sleep Questionnaire three-item index (PSQ3)

PSQ3 is a three-item PRO assessing 'trouble falling asleep because of pain', 'frequency of awakenings by pain during the night' and 'frequency of awakenings by pain in the morning' on the visual analogue scale with one week recall period. The items of PSQ3 are also part of the Pain and Sleep Questionnaire (PSQ) and Chronic Pain Sleep Inventory (CPSI). The assessment of selected psychometric properties of PSQ-3 using the data from clinical studies in different chronic pain indications is reported by Ayearst et al (35). PSQ-3 questionnaire will be completed during the site visits in eDiary.

8.6.4 Other Biomarkers

In addition to the biomarkers described above, further biomarkers related to, e.g., the mode of action or the safety of the study intervention and similar compounds may be investigated. The same applies to further biomarkers deemed relevant to endometriosis and associated health problems. These investigations may include e.g. diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers.

8.7 Immunogenicity Assessments

Not applicable

8.8 Health Economics

Health-economic parameters are evaluated through PROs EQ-5D-5L and mWPAI (Section 8.1.1) to assess utility and activity/productivity impairment. Descriptive PRO analyses will be part of clinical report, additional economic analyses including country-specific cost and utility estimation are planned in a separate HEOR analysis and report.

9. Statistical Considerations

9.1 Statistical Hypotheses

The objective of the primary analysis is the detection of a trend in the relationship between the dose of BAY 1817080 and the primary efficacy endpoint, and describing the dose-response-relationship to provide a dose for possible phase III studies. Thus, only the placebo group (0 mg of BAY 1817080) and the three active intervention groups of BAY 1817080 with corresponding doses $d_j, j = 1, \dots, 4$, will be used for the primary efficacy assessment. The objective will be pursued through the application of the MCP-Mod approach, because there is not enough prior knowledge to decide on a specific dose-response-model $f(d, \boldsymbol{\theta})$. The MCP-Mod method makes "use [of] multiple comparison techniques to choose the most likely [parametric model among a set of candidates] to represent the underlying dose-response curve" (36). It combines the flexibility of modeling with the robustness to model misspecification associated with multiple comparison procedures.

For the so-called proof of activity of BAY 1817080, at least one of the null hypotheses

$$H_{0m}: \sum_{j=1}^{4} c_{mj}\, f(d_j, \boldsymbol{\theta}_m) = 0,$$

$\sum_{j=1}^{4} c_{mj} = 0$, belonging to model m has to be rejected. The contrast coefficients c_{mj} are chosen such that they maximize the local power, i. e. the probability for rejecting the null hypothesis H_{0m} under the one-sided alternative hypothesis

$$H_{1m}: \sum_{j=1}^{4} c_{mj}\, f(d_j, \boldsymbol{\theta}_m) > 0.$$

Consequently, the null hypothesis H_{0m} states no trend in the dose-response-relationship (implying the overall null hypothesis of no trend in even one model) since the chosen dose-response-curves described in Section 9.4 are monotonically decreasing. The optimal contrast coefficients depend on the sample sizes in the end.

A more detailed description of the multiple comparison procedure modelling (MCP-Mod) approach and the models used will be given in Section 9.4.

9.2 Sample Size Determination

Approximately 840 participants will be screened to start study intervention in about 420 randomized participants for at least 50 participants evaluable for the primary analysis (i.e. included in the pPPS) per intervention group. The primary analysis will not include the participants enrolled based on visually-confirmed diagnosis, i.e. about half of the women randomized in Japan, nor all the participants randomized in China, who are mainly included to generate further data using the ESD in this population. Refer to Section 9.3 for further information of inclusion of participants into analysis sets.

If blinded data reviews indicate an unexpected high number of screening failures due to the COVID-19 pandemic, enrollment may be increased.

Sample size calculations were performed for establishing evidence of a drug effect across the doses, that is, detecting a statistically significant dose response signal for the primary efficacy outcome in this study using the MCP-Mod approach. They are based on the following assumptions:

- change in mean EAPP under placebo after 12 weeks of -2.3
- maximum change in mean EAPP of -1.2 for BAY 1817080 over placebo
- standard deviation of 2.5 for all dose groups
- a set of plausible dose-response shapes including Emax and sigmoidal Emax models (chosen based on literature review and historic in-house data)
- random allocation of participants to dose groups according to a 1:1:1:1 ratio,

A sample size of 50 participants per dose groups will have appr. 90% power (averaged across the set of dose-response shapes) to demonstrate a dose- response relationship, using a one-sided test at a type I error rate of α=0.10.

Approximately 70 participants for primary analysis will be randomized to each treatment group to achieve 50 evaluable participants for each treatment group.

In addition, 28 participants from Japan with clinical diagnosis, as well as 28 participants from China will be randomized 1:1:1:1, but will not be included in the primary analysis.

Although not formally included in the sample size determination, the exploratory elagolix 150mg treatment group is planned to be of about the same size as the other treatment groups. As participants from Japan and China cannot be randomized to the elagolix 150mg arm, the randomization ratio outside of Japan and China will be 3:3:3:3:4 (Placebo:25 mg:75 mg:150 mg:elagolix). This will provide similar sizes of all treatment groups overall.

9.3 Analysis Sets

Final decisions regarding the assignment of subjects to analysis sets defined in table 1 will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to analysis set(s).

Table 9–1: Definition of the analysis sets.

Analysis set	Description
Enrolled	All participants who signed the informed consent form
Full Analysis Set (FAS)	All randomized non-Chinese participants
Primary full Analysis Set (pFAS)	All randomized non-Chinese participants with surgically-confirmed endometriosis
Per Protocol Set (PPS)	All randomized non-Chinese participants without any validity findings impacting the primary efficacy variable
Primary Per Protocol Set (pPPS)	All randomized non-Chinese participants with surgically-confirmed endometriosis and no validity finding impacting the primary efficacy variable
Safety Analysis Set (SAF)	All participants who took at least 1 dose of study drug
Pharmacokinetic Analysis Set (PKS)	All participants who took at least 1 dose of study drug and had at least 1 available pharmacokinetic sample

The primary analysis will be based on the pPPS. The PPS will be used for other non-safety analyses and the separate pharmacodynamics analyses. Safety analyses will be performed on the SAF. If and only if the SAF is used, the subjects will be analyzed as treated instead of as randomized. In selected cases, the (p)FAS will be used for sensitivity analyses. PK analysis will be performed on the PKS. Data from screening failures will only be shown in separate listings.

9.4 Statistical Analyses

The statistical analysis plan will be finalized prior to unblinding and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. If not otherwise indicated, the statistical analyses will be performed using SAS; the version used will be specified in the statistical analysis plan.

9.4.1 General Considerations

According to the statistical hypotheses above, the detection of a trend in the dose-response relationship between BAY 1817080 and EAPP will be of a one-sided nature. The level of significance for statistical testing is set to 10 % to control the overall type I error, i.e. the type I error will be controlled for the primary analysis only. No multiplicity problem arises from the interim analyses. This study will be independent from their conduct and results, including different teams in order to maintain the blind of the study team.

In general, CIs will be two-sided. Thus, the CIs belonging to or directly linked with the primary analysis will have a coverage probability of 80 %. In addition, 95 %-CIs will be provided. Otherwise only 95 %-CIs will be calculated.

Baseline will be the last measurement or the measurements of the last 28 days before randomization.

The four study periods are defined in section 1.3.

9.4.2 Primary Endpoint(s)

The primary estimand, including the primary efficacy variable, is described in section 3. The handling of missing values unrelated to the ICEs mentioned there will be described in the SAP.

The dose-response effect-capturing parameters μ_{d_j} of the probability model assumed for the participant responses are assumed to follow the statistical model

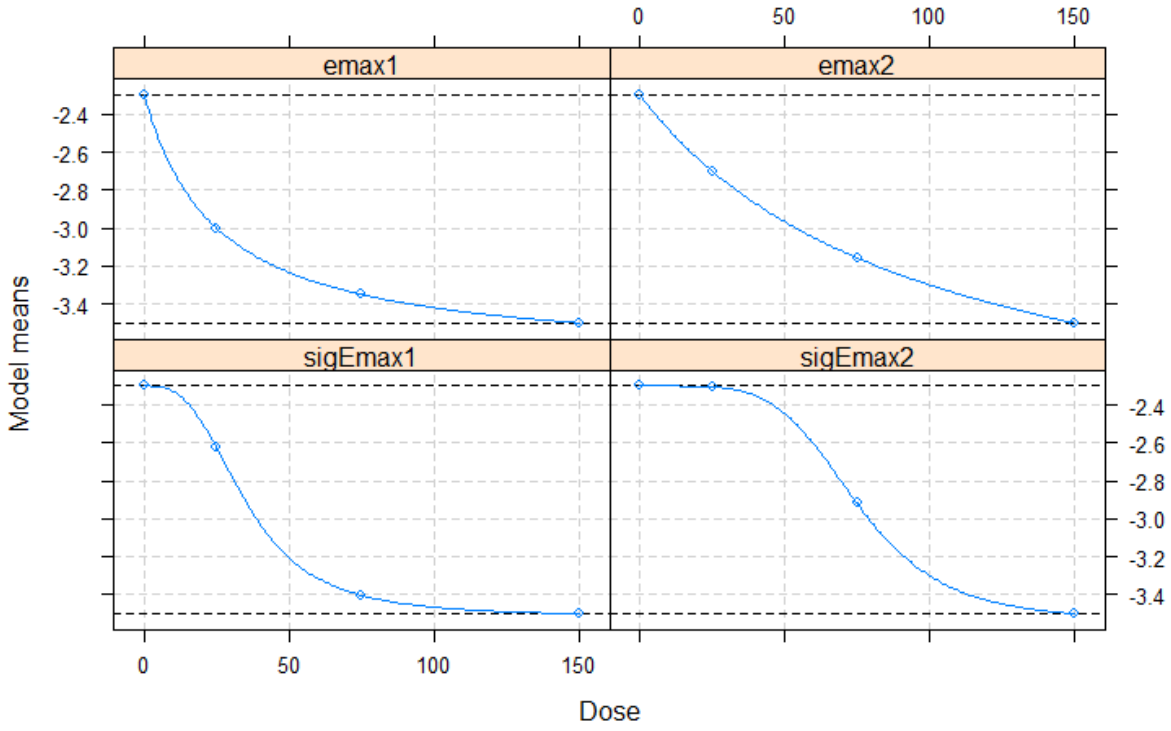
$$\mu_{d_j} = f(d_j, \boldsymbol{\theta}) + \boldsymbol{\varepsilon}_j, \quad j = 1, \ldots, 4,$$

where $\boldsymbol{\varepsilon} \sim \mathcal{N}(\mathbf{0}, \boldsymbol{S})$ and $f(d, \boldsymbol{\theta}) = -2.3 + E_{max} d^{\eta} / \left(ED_{50}^{\eta} + d^{\eta}\right)$ defining the dose-response models in the candidate set, where d is the dose ranging from 0 mg to 150 mg. The different models are characterized by the parametrization $\boldsymbol{\theta}$ listed in Table 9–2. Figure 9–1 illustrates them.

Table 9–2: Parameters of the dose-response-curves in the candidate set.

Model		Parameters		
Abbreviation	Indicator $\boldsymbol{m}$	$\boldsymbol{ED_{50}}$	$\boldsymbol{E_{max}}$	Hill factor $\boldsymbol{\eta}$
emax1	1	25	-1.4	1
emax2	2	100	-2.0	1
sigEmax1	3	35	-1.2	3
sigEmax2	4	75	-1.2	5

Figure 9–1: Candidate set of dose-response-curves.



The null hypothesis of no trend in even one model will be investigated by means of the maximum of the test-statistics belonging to one-sided single contrast tests challenging H_{0m}. The critical value will be chosen such that the multiple significance level of 0.1 will be met.

If at least one local test-statistic is greater than the global critical value, the model m^* with the highest Akaike's Information Criterion among the significant models will be fitted for determining the smallest dose which shows a clinically relevant and a statistically significant effect, i.e.

$$MED = \underset{d \in \{25,50,\ldots,150\}}{\operatorname{argmin}} \{f(d, \boldsymbol{\theta}_{m^*}) > f(d_1, \boldsymbol{\theta}_{m^*}) + \Delta\},$$

where Δ is the smallest relevant difference, by which a dose is expected to be better than placebo. The smallest relevant difference will be defined in the SAP prior to un-blinding to account for the most up-to-date research.

9.4.3 Secondary Endpoint(s)

For the identification of at least 1 superior effective dose of BAY 1817080 compared to placebo in terms of the absolute change in mean worst EAPP from baseline to end of intervention, pairwise p-values and 80 % as well as 95 % CIs will be derived from an ANCOVA. The mean worst EAPP at baseline and the region (Japan vs. ROW excluding China) are set as covariates.

The secondary endpoint of TEAEs will be analyzed by descriptive statistics, such as frequency tables. A TEAE is defined as any event arising or worsening after the start of study drug administration until 14 days after the last study medication intake. All TEAEs will be tabulated according to the affected system organ class and preferred term, as coded by the

Medical Dictionary for Regulatory Affairs. Further tables will be provided for serious and/or drug related TEAEs.

Summaries will be provided by intervention group and overall.

9.4.4 Other Endpoints

The analysis of the exploratory endpoints will be described in the SAP.

9.4.5 Safety Analysis

All safety analyses will be descriptive, and will be performed on the SAF. Details on safety analyses will be described in the SAP.

9.4.6 Other Analysis

BAY 1817080 plasma concentrations will be summarized by group, visit and planned sampling time. The statistical analysis will be described in the SAP.

Population PK/PD and selected biomarker exploratory analyses will be described in separate analysis plans. The population PK/PD analysis will be presented separately from the main clinical study report.

PRO data will be used for psychometric analyses of ESD and EIS, which will be conducted and reported outside of clinical analyses and report.

Any other pre-specified analyses will be described in the SAP finalized before database lock.

9.5 Interim Analysis

Interim analyses may be performed after approximately 50% of the study participants have completed the 12-week intervention period in order to plan subsequent studies. This study will be independent from their conduct and results, including different teams in order to maintain the blind of the study team. For this, even if some interim analyses may be described in the main SAP, separate table, listings and figures documents will be created.

The Statistical Analysis Plans, including the Biomarker SAP and the HEOR SAP, will describe the planned interim analyses in greater detail. No formal interim report will be written.

The results of the biomarker investigation and of the HEOR analysis may be reported separately (see Section 8.6 and Section 8.8 for details)

10. Supporting Documentation and Operational Considerations

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

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with 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 Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations

- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Any substantial modification of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH Good Clinical Practice and national and international regulations.
- 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 site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information 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.

10.1.3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant 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, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- 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 re-consented to the most current version of the ICF(s) during their participation in the study.

- A copy of the ICF(s) must be provided to the participants.
- Participants who are rescreened are required to sign a new ICF.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records datasets or biological samples 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.
- Participants will be asked to register with their contact information (email address) as users for the eDiary. This information is managed by the service provider and data is transferred to the sponsor using identifier only.
- The service provider(s) will treat participants' personal data in a confidential manner according to the regulations.
- The participant must be informed that his/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 his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees Structure

A Study Steering Committee will be established to provide medical consultancy. The full description of the Steering Committee structure and tasks is provided in the Steering Committee charter.

10.1.6 Dissemination of Clinical Study Data

- Result Summaries of Bayer's sponsored clinical trials in drug development Phases 2, 3 and 4 and Phase 1 studies in patients are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition, results of clinical drug trials will be provided on the publicly funded website www.ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.
- Bayer commits to sharing, upon request, from qualified scientific and medical researchers' patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients, for medicines and indications approved in the United States and European Union on or after January 01, 2014 as necessary for conducting legitimate research.

- All Bayer-sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF Completion Guidelines.
- 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 integrated data review 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 important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (e.g., 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 noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- 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.

10.1.8 Source Documents

- 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 reported on the CRF or 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.
    - Definition of what constitutes source data can be found in Source Data Location List.

- 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 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.

10.1.9 Study and Site Start and Closure

First Act of Recruitment

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

The first act of recruitment is the first subject screened in the study and will be the study start date.

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 intervention development

For 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 contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

- 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 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.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10–1 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 intervention 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 intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Blood samples for testing of liver parameters, i.e., AP, ALT (GPT), AST (GOT), Gamma-GT, and total bilirubin, should be taken as specified in the SoA. These visits are not to be performed in participants randomized to the active comparator elagolix.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- For pregnancy tests, see the SoA Section 1.3 and Section 8.3.5
- ATIII activity: Increases up to 30% above baseline value were observed in healthy subjects and chronic cough patients in study 18184. Since there is no established clinical relevance linked to increased ATIII activity in medical literature, it is concluded that at this stage of development, the increase in ATIII activity can be considered as not clinically relevant. Screening ATIII results will be available to the investigator/sites as soon as measured and reported by the central laboratory. Considering the potential for unblinding participants receiving active treatment with BAY 1817080, the results of ATIII measures at the following visits will not be communicated to study teams nor investigators until after unblinding of the study.

Table 10–1: Protocol-Required Safety Laboratory tests

Panel	Parameters	Time point(s)	Comment
Safety parameter			
Biochemistry	Albumin	Visits 1a, 2-7	eGFR (MDRD formula) calculation needed for Visit 1a only
	Calcium		
	Magnesium		
	Creatinine		
	Cystatin C		
	Phosphorus		
	Potassium		
	Sodium		
	Total protein		
	Blood urea nitrogen		
	Alkaline phosphatase		
	ALT		
	AST		
	GGT		
	Total bilirubin		
	Total bile acids		
	Lipase		
	Pancreatic α-amylase		
	Non-fasting glucose		
	Total cholesterol		
	HDL-cholesterol		
	LDL-cholesterol		
	Triglycerides		
	β-hCG		
	Ferritin		
Hematology	Erythrocytes	Visits 1a, 2-7	
	Hematocrit		
	Hemoglobin		
	Leukocytes with differentials (neutrophils, lymphocytes, monocytes, eosinophils, basophils)		
	Platelets		
	Hemoglobin A1c	Visits 1a, 2-7	
Coagulation	aPTT		
	Fibrinogen		
	INR		
	PT (Quick)		
	Antithrombin III (ATIII)	Visits 1a, 2-7	Reporting of the results at the screening phase only, other results reported to sites after the database lock
Hormones	Estradiol Progesterone[a]	Visits 1a-7	
SARS-CoV-2	SARS-CoV-2 viral antibody test (IgM, IgG)	Visits 1a, 6/7	Depending on which is the last Follow-up visit for the participant
SARS-CoV-2	RNA test	if needed	in case of symptoms, see below
Highly sensitive serum pregnancy test	β-hCG	Visits 1a, 2	

Table 10–1: Protocol-Required Safety Laboratory tests

Panel	Parameters	Time point(s)	Comment
Highly sensitive urine pregnancy test	β-hCG	Visits 1a, 2-7	
Screening/Start of Intervention parameters			
Virology	Hepatitis B virus surface antigen	Visit 1a	HCV-mRNA automatically tested if anti-HCV is positive
	Hepatitis C virus antibodies		
	Hepatitis C virus mRNA		
Cervical cytology	Cervical smear	Visit 1a	HPV-DNA automatically tested if ASCUS is reported from cervical cytology
	High risk HPV-DNA		
Hormones	Thyroid stimulating hormone	Visit 1a	
	Luteinizing hormone	Visit 1a	
	Follicle-stimulating hormone	Visit 1a	
BM, PK & PG			
Biomarker (BM)	Biomarkers	Visits 1a, 2-6	Delivered from the central laboratory to the BM laboratory
Endometriosis biomarkers	Cancer antigen 125 (CA125), Carbohydrate antigen 19-9 (CA19-9), Beta-2-Microglobulin (B2M)	Visits 1a, 2-6	Delivered to central laboratory
Pharmacokinetics (PK)	Pre-dose PK	Visits 2-5	Delivered from the central laboratory to the PK laboratory
	Post-dose PK at 2h & 4 h after study intervention	Visits 2 and 5 at Visit 4 5h after study intervention	
Pharmacogenetics (PG)	Genetics	One sample at Visit 2 or 3	Only consented participants Delivered from the central laboratory to the PG laboratory
Supplies to be provided to study participants			
Urine pregnancy tests	To be used at home	Per need	
Spermicide-coated condoms	To be used at home	Per need	
Per need triggered parameters			
Repeated test triggered by abnormal (out of range) test result	Dependent on result	Per need	Repeat once

a Blood samples should be taken at least 72 hours after the intake of high doses of biotin, since the laboratory results of ferritin and progesterone may be affected, if a participant had biotin intake at a concentration higher than 5 mg per day which occurred less than 72 hours before the sample is taken.

Abbreviations: A1AT = alpha-1 antitrypsin; ALT = alanine-aminotransferase; aPTT = Activated partial thromboplastin time; ASCUS = Atypical squamous cells of unknown significance; AST = aspartate-aminotransferase; β-hCG = β-human chorionic gonadotropin; BM = biomarker; CK = creatine kinase; DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyl transferase; HCV = hepatitis C virus; HDL = high-density lipoprotein; HPV = human papilloma virus; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = Low-density lipoprotein; MDRD = Modification of Diet in Renal Disease; mRNA = messenger ribonucleic acid; PCR = polymerase chain reaction; PG = pharmacogenetics; PK = pharmacokinetics; PT = prothrombin time; ULN = upper limit of normal; WBC = white blood cells

Investigators must document their review of each laboratory safety report.

SARS-CoV-2 Testing

Testing for SARS-CoV-2 virus RNA is to be performed in case a participant reports Covid-19 associated symptoms, including fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or running nose, nausea or vomiting, diarrhea, during the study.

RNA tests will be provided centrally to ensure that they can actually be performed and to avoid unnecessary efforts by participants/sites in countries where there is no easy access to the test, even if symptoms are present.

If required by local guidelines/practice for SARS-CoV-2 infection screening/diagnosis, additional laboratory or imaging examinations can be done, e.g. chest computed tomography. The results should be documented in the medical records.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

Time period and frequency for collecting AEs and SAEs can be found in Section 8.3.1

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, that occurs after providing written informed consent, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of

sequelae.

- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. “Lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the 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 (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any AE that, at any dose:

a. Results in death

b. Is life-threatening

- The term 'life-threatening' in the definition of 'serious' refers to an event in which the 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 (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e.	**Is a congenital anomaly/birth defect**
f.	**Other situations:** • Medical or scientific judgment should be exercised 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.

10.3.3 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 (e.g., 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 sponsor in lieu of completion of the required form. • There may be instances when copies of medical records for certain cases are

requested by the sponsor. 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.

- 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 Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- 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 study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of 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 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.
- If a participant dies during participation in the study, the investigator will provide the sponsor with a copy of any post mortem findings including histopathology
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data transmission (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the local pharmacovigilance contact person by telephone.
- Contacts for SAE reporting can be found in the Investigator Site File.

SAE Reporting to the Sponsor via Paper Data Collection Tool

- Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to the sponsor's Pharmacovigilance department.
- In rare circumstances and if email transmission is not feasible, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does data collection tool pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator Site File.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Contraceptive Guidance

- All participants in this study are considered to be of child-bearing potential, and accordingly must use contraception during the entire study participation
- Participants must be willing to use a non-hormonal barrier method for contraception (spermicide-coated condoms for their partners) from screening visit until the end of the study (or for at least 2 weeks after the last dose of study intervention in case of withdrawal from the study). This is not required if adequate contraception is achieved by at least one of the following options:
  - vasectomy of male partner(s)
  - female sterilization through bilateral salpingectomy or tubal ligation/occlusion
  - use of copper IUD for at least 6 months at Visit 1a, provided that the copper IUD is planned to be worn without replacement for the entire study duration
  - total abstinence from heterosexual intercourse, which is only to be chosen if this method of contraception is consistent with the preferred and usual lifestyle of the participant; periodic abstinence and coitus interruptus (withdrawal) are not meant by total sexual abstinence
- For discontinuation of hormonal contraceptives, see Section 6.8.2.2.

Collection of Pregnancy Information:

- The investigator will collect pregnancy information on any participant who becomes pregnant while participating in this study (or within 2 weeks of the last dose of study intervention, in the case of premature discontinuation during the intervention phase). The initial information (at a minimum: participant identification, description of study intervention and report source) will be recorded on the appropriate form and submitted to the sponsor 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. 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 for medical reasons will be reported as an AE or SAE.
  - A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) 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 intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

  Any participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5 Appendix 5: Genetics

- Genetic predisposition has been proposed to correlate with disease severity and pain processing in endometriosis (37). In needs to be explored whether some of the recently discovered genetic variants contribute to pain experience and response to therapy in endometriosis.
- Genetic predisposition that might be associated with treatment response to BAY 1817080 and/or pain experience in endometriosis will be investigated as a voluntary substudy.
- The participation in the pharmacogenetic (PG) substudy is voluntary and has no influence on the participation in the main study.
- A whole blood sample will be obtained from those participants, who have signed a separate informed consent form (ICF) for PG substudy. The sample may be used as source of germline DNA.
- DNA will be utilized for genotyping of candidate genes suggested to play a role in endometriosis and/or pain processing.
- Analyses may include targeted sequencing of the candidate genes and allele-specific polymerase chain reaction analyses, for example. The methods will be chosen according to current state of the art.
- Details on the collection and handling of samples will be provided in separate documents (sample handling sheets and laboratory manual), available at the Investigator Site File.
- Samples may be stored for a maximum of 15 years (or according to local regulations) following the end of the study at a facility selected by the sponsor to enable further analyses.
- The results of PG analyses may be reported separately (e.g. in a Biomarker Evaluation Report).

10.6 Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

10.6.1 Liver safety -related monitoring and discontinuation criteria

Investigators and participants should pay special attention to non-specific symptoms which may be associated with liver dysfunction; including anorexia, nausea, fatigue, right upper abdominal discomfort, vomiting, malaise, jaundice, fever, and rash.

- Information on these symptoms should be asked for in case of abnormal liver laboratory values (see Table 10–2) or any other suspicion of liver dysfunction.
- Participants should be regularly reminded to contact the investigator immediately if they are concerned about such symptoms, and unscheduled visits for evaluation should be considered

Table 10–2: Liver Safety-Related Monitoring and Discontinuation Criteria

Lab result	Measures
ALT or AST ＞ 3 x ULN	• Initiate close observation as defined in Section 10.6.2. • Consider withdrawal of study intervention if the participant does not adhere to procedures required for close observation[a]
ALT or AST > 3 x ULN **and** TBL > 2 x ULN	Withdraw study intervention
ALT or AST > 3 x ULN **and** INR > 1.5 x ULN	Withdraw study intervention
ALT or AST > 3 ULN **with** appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)	Withdraw study intervention
ALT or AST > 5 x ULN for more than 2 weeks	Withdraw study intervention
ALT or AST > 8 x ULN	Withdraw study intervention

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR= international normalized ratio, TBL = total bilirubin, ULN = upper limit of normal (all referring to serum/plasma)

a in case visits for close observation could not be arranged with a frequency deemed adequate by the investigator, despite of reasonable efforts

10.6.2 Close observation of participants with ALT or AST ＞ 3 x ULN

- Abnormal laboratory results and clinical signs and symptoms resulting in close liver observation should be reported as adverse event.
- Abnormal laboratory results meeting the criteria of transaminases (ALT and/or AST) >8x ULN or >3x ULN with total bilirubin >2x ULN will be reported as AEs of special interest (see Section 8.3.7).
- It is critical to initiate close observation immediately upon detection and confirmation of early signals of possible drug-induced liver injury, and not to wait until the next scheduled visit or monitoring interval
- Procedures to be taken resemble workup/ documentation along the guideline of the US FDA for assessment of potential drug-induced liver injury (38). Objectives are to:

- Ensure participant safety
- Identify possible non-study-intervention-related causes of liver injury

- A close observation has to be initiated during intervention or follow-up phase if ALT or AST reaches >3 x ULN. Close observation includes:
  - Sampling for the first batch of laboratory parameters (see Table 10–3).
  - Repeating follow-up samplings (see Table 10–3).2 to 3 times per week. Frequency of retesting can decrease to once a week or less if abnormalities stabilize.
  - Obtaining a detailed history of the symptoms and prior or concurrent diseases
  - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
  - Ruling out acute viral hepatitis, autoimmune or alcoholic hepatitis, nonalcoholic steatohepatitis, hypoxic/ischemic hepatology and biliary tract disease. This may require performing additional procedures, e.g. ultrasound examinations. If requested, tests will be done retrospectively using residual blood/serum samples collected at visits before laboratory abnormalities occurred.
  - Obtaining a history of exposure to environmental chemical agents
  - Obtaining additional tests to evaluate liver function as required (e.g. INR, direct bilirubin measurements)
  - Liver imaging
  - Considering gastroenterology or hepatology consultations
- Data for any findings are to be recorded in the corresponding eCRF pages
- Stopping criteria for close observation:
  - 2 consecutive normal/baseline results for liver enzymes in addition to availability of results from detailed close liver observation lab panel, related procedures, relevant medical and medication history and the reporting of signs and symptoms related to elevated liver enzymes, or
  - A confirmed clinical diagnosis explaining the elevated liver enzymes.

Table 10–3: Samples during close observation for liver safety

Parameters	Time point(s)	Comment
First batch of parameters to be taken when initiating close observation for liver safety		
Albumin	Per need	First sample after AST or ALT > 3 X ULN
Alkaline phosphatase (AP)		
Alanine-aminotransferase (ALT)		
Aspartate-aminotransferase (AST)		
Complete blood count including WBC with differentials		
Cholinesterase		
Conjugated (direct) bilirubin		
Creatine kinase (CK)		
GGT		

Table 10–3: Samples during close observation for liver safety

Parameters	Time point(s)	Comment
Hemoglobin		
INR		
Lactate dehydrogenase (LDH)		
PT		
Total bilirubin		
HDL-cholesterol		
LDL-cholesterol		
Total cholesterol		
Triglycerides		
Anti-hepatitis A virus IgM antibodies.		
Hepatitis B virus surface antigen (if positive, automatically test below antibodies related to HBV and HDV) - Anti-hepatitis B surface antibodies - Anti-hepatitis B core total antibodies - Anti-hepatitis B IgM antibodies - Hepatitis B PCR (viral copies) - Hepatitis D virus antibodies (if positive, automatically test HDV RNA)		
Anti-hepatitis C virus antibodies (if positive, automatically test Hepatitis C viral copies) HCV RNA		
Anti-Hepatitis D virus antibodies (if positive, automatically test HDV RNA)		
Anti-hepatitis E virus IgM (if positive, automatically test HEV RNA)		
Anti-cytomegalovirus (CMV) IgM antibodies		
Anti-Epstein-Barr Virus (EBV) IgM antibodies		
Herpes simplex IgM (anti-HSV IgM)		
IgG level (gamma globulins)		
IgA		
IgM		
c-Antineutrophil cytoplasmic antibodies		
c-Antineutrophil perinuclear antibodies		
Anti-mitochondrial antibodies		
Anti-nuclear antibodies (ANA)		
Anti-Smooth muscle antibodies (ASMA)		
A1AT level		
Ceruloplasmin		
Ferritin		
Iron		
Total iron binding capacity		
Follow-up samples during close observation for liver safety		
Albumin	Per need	Additional parameters/tests may be added as medically justified
Alkaline phosphatase (AP)		
Alanine-aminotransferase (ALT)		
Aspartate-aminotransferase (AST)		
WBC with differentials		
Cholinesterase		

Table 10–3: Samples during close observation for liver safety

Parameters	Time point(s)	Comment
CK		
Conjugated (direct) bilirubin		
Total bilirubin		
GGT		
INR		
LDH		

A1AT = Alpha-1 antitrypsin; CK = Creatine kinase; DNA = deoxyribonucleic acid; GGT = Gamma-glutamyl transferase; INR = International normalized ratio; HBV = hepatitis B virus; HDL = high-density lipoprotein; HDV = hepatitis D virus; HEV = hepatitis E virus; HSV = herpes simplex virus; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; LDH = lactate dehydrogenase; LDL = low density lipoprotein; PCR = Polymerase chain reaction; PT = prothrombin time; RNA = ribonucleic acid; ULN = upper limit of normal; WBC = white blood cells

10.7 Appendix 7: Examples of Most Common Medication Regarded as Strong CYP3A4 Inhibitors or Inducers

Table 10–4 lists the most common prohibited medication regarded as strong CYP3A4 inhibitors or inducers.

Table 10–4: Cytochrome P450 (CYP) 3A4: List of most common prohibited concomitant medication

Strong CYP3A4 inducers, e.g.	Strong CYP3A4 inhibitors, e.g.
apalutamide	boceprevir
avasimibe	clarithromycin
carbamazepine	cobicistat
carbamazepine	conivaptan > 20 mg
enzalutamide	danoprevir / ritonavir
fosphenytoin	elvitegravir / ritonavir
hypericum perforatum / St John's wort	grapefruit juice
mephenytoin	indinavir, indinavir / ritonavir
mitotane	itraconazole
phenytoin	ketoconazole
rifapentine	lopinavir / ritonavir
rifampicin / rifampin	nefazodone
	nelfinavir
	posaconazole
	ritonavir
	saquinavir, saquinavir / ritonavir
	telaprevir
	telithromycin
	tipranavir / ritonavir
	troleandomycin
	voriconazole

Source: Drug Interaction Solutions by University of Washington, July 2020 (39)

Weak or moderate inducers or inhibitors of CYP3A4 are allowed. Table 10–5 gives examples of the most relevant antibiotics, antimycotics and antidepressants regarded as weak or moderate CYP3A4 inhibitors or inducers. For further information contact the sponsor.

Table 10–5: Cytochrome P450 (CYP) 3A4: List of most common allowed concomitant medication

Weak or Moderate CYP3A4 inducers, e.g.	Weak or Moderate CYP3A4 inhibitors, e.g.
dicloxacillin	alprazolam
clobazam	azithromycin
isavuconazole	casopitant
oritavancin	ciprofloxacin
rifabutin	clotrimazole
nafcillin	erythromycin
flucloxacillin	fluconazole ≤ 200 mg
	fluvoxamine
	isoniazid
	lefamulin
	norfloxacine
	rimegepant
	roxithromycin

Source: Drug Interaction Solutions by University of Washington, July 2020 (39)

10.8 Appendix 8: Actigraphy Substudy

- Studies suggest that 50% to 70% of chronic pain patients suffer from a sleep disturbance. Little is known about sleep in endometriosis patients, but individual studies hint towards reduced sleep quality.
- Participants in this study suffer from chronic pain due to endometriosis with high pain score at the begin of the intervention. Investigation of sleep quality is considered as option for an additional variable demonstrating improvement of patient outcomes.
- Participants will be offered a possibility to participate in an optional actigraphy substudy on sleep quality in endometriosis, potential associations with pain symptoms and intervention-related improvement of bad sleep.
- The participation in the substudy is voluntary and has no influence on the participation in the main study. For this substudy approximately 125 evaluable participants (approximately 25 per treatment group) are required. For this reason, the sponsor reserves the right to limit participation in this substudy to certain countries. Such limitation will be communicated to the relevant authority at the time of submission of the study.
- Actigraphy will be monitored at defined time points during screening and study intervention periods as specified in the SoA with a medical-grade wearable monitoring device. This wrist worn wearable is a Class I non-measuring medical device within the European Union and an FDA cleared Class II medical device within the United States.

- The actigraphy monitoring device will capture and record raw accelerometer data, which will be used to derive markers of mobility during sleep and daily activity, such as but not limited to:
  - total minutes asleep
  - sleep effectiveness
  - sleep onset latency
  - awakenings
  - physical activity intensity
  - activity bouts
  - sedentary bouts
- Site personnel will be trained for the use of the wearable actigraphy monitoring device during the Investigator's Meeting and/or during the Site Initiation. The instructions for the use of the device will be provided in the Investigator Site File.
- Site personnel will provide technical support for the study participants. In addition, help desk will be available.
- Study participants will be asked to use the actigraphy monitoring device for two periods of time (24-hours/day) during the study:
  - During screening period (baseline measurement) for all days between Visits 1a and 2
  - During the third month of intervention, for all days between Visits 4 and 5.
- In an exploratory BM analysis, different parameters characterizing sleep quality will be investigated retrospectively (e.g. total sleep time, sleep onset latency, sleep efficiency) and daily activity (e.g. number of steps taken, physical activity intensity, sedentary bouts)
- The results will be reported separately (e.g. in a Biomarker Evaluation Report).

10.9 Appendix 9: Country-specific Requirements

10.9.1 Japan

- Limited to no more than half of all randomized Japanese participants: For inclusion in the study visually-confirmed endometriosis diagnosis can be based on previous imaging (i.e. endometriosis lesion detected by ultrasound or MRI). If the participant was diagnosed by ultrasound, the lesion must be visualized again by ultrasound at the screening visit. If the participant was diagnosed by MRI, the diagnosis must have been made within 12 months before Visit 1a.
- The estimation of GFR is limited by differences in creatinine generation among ethnicities. Thus, the MDRD GFR equation is less accurate for Asians, with greater bias at eGFR less than 30 mL/min/1.73 m^2. In Japan, the equation recommended by the Japanese Society of Nephrology (40) will be used for participants enrolled at Japan site in this study.

- $eGFRcreat(mL/min/1.73m^2) = 194 \times Cr^{-1.094} \times age^{-0.287} \times 0.739$

- The investigator must report immediately all non-approved medical device failures which could cause health damage, as well as any health damage that may be causally associated with a non-approved medical device failure. For this reporting, the forms provided are to be used and sent to the designated recipient.
- Participants in Japan will not be randomized to receive elagolix.

10.9.2 China

- Participants in China will not be randomized to receive elagolix.
- Genetic and non-genetic biomarkers samples will not be performed in China.

10.10 Appendix 10: Abbreviations

A1AT	Alpha-1 antitrypsin
AE(s)	Adverse event(s)
AG	Aktiengesellschaft, public limited company
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
ASCUS	Atypical squamous cells of unknown significance
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
ATIII	Antithrombin III
BCRP	Breast cancer resistance protein
BID	Bis in die (twice daily)
B2M	Beta-2-Microglobulin Biomarker
BM(s)	Biomarker(s)
CA125	Cancer antigen 125 biomarker
CA 19-9	Carbohydrate antigen 19-9
CD(s)	Compact disc(s)
CI(s)	Confidence interval(s)
CK	Creatine kinase
COC(s)	Combined oral contraceptive(s)
COVID-19	Coronavirus disease of 2019
CRF(s)	Case report form(s)
CTFG	Clinical Trial Facilitation Group
CYP3A4	Cytochrome P450 isoenzyme 3A4
DBP	Diastolic blood pressure
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
EAPP	Endometriosis associated pelvic pain
eCRF(s)	Electronic case report form(s)
eDiary	Electronic patient diary
eGFR	Estimated glomerular filtration rate
EIS	Endometriosis Impact Scale
ePRO	Electronic patient report outcome
EQ-5D-5L	EuroQoL 5-dimension 5-level questionnaire
ESD	Endometriosis Symptom diary
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GLDH	Glutamate dehydrogenase
GnRH	Gonadotropin-releasing hormone

GnRH-a	Gonadotropin-releasing hormone agonist
HbA1G	Hemoglobin A1c
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HCV-mRNA	Hepatitis C virus mRNA
HDL	high-density lipoprotein
HDV	Hepatitis D virus
HEOR	Health economics and outcomes research
HEV	hepatitis E virus
HFHC	high fat, high calorie
HPV	Human papilloma virus
HR	Heart rate
HSV	Herpes simplex virus
i.e.	*id est,* (that is)
IB	Investigator's Brochure
ICE(s)	Intercurrent event(s)
ICF(s)	Informed consent form(s)
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC(s)	Independent Ethics Committee(s)
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IND	Investigational new drug
INR	international normalized ratio
IRB(s)	Institutional Review Board(s)
IUD	Intrauterine device
IWRS	Interactive web response system
LDH	lactate dehydrogenase
LDL	Low-density lipoprotein
MCP-Mod	Multiple Comparison Procedures – Modelling
MD	Medical Doctor
MDRD	Modification of Diet in Renal Disease
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
mWPAI	Modified Work Productivity and Activity Impairment questionnaire
NA	Not applicable
NCT	ClinicalTrials.gov identifier
NRS	Numerical rating scale
OATP	Organic anion transporting polypeptide
OATP 1B1	Organic anion transporting polypeptide B1
OATP 1B3	Organic anion transporting polypeptide B3
P2X	Purinergic receptor
P2X2/3	Purinergic receptor 2/3
P2X3	Purinergic receptor 3
P2Y	Purinergic receptor Y

PCR	Polymerase chain reaction
PCS	Pain catastrophizing score
PD	Pharmacodynamic(s)
pFAS	Primary full Analysis Set
PG	Pharmacogenetic
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PIF	Photoirritation factor
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic Analysis Set
PopPK	Population pharmacokinetics
pPPS	Primary Per Protocol Set
PPS	Per protocol set
PRO(s)	Patient reported outcome(s)
PSQ3	Pain and Sleep Questionnaire three-item index
PT	Prothrombin time
QD	*quaque die*, daily
QTLs	Quality tolerance limits
RNA	Ribonucleic acid
RO	Receptor occupancy
SAE(s)	Serious adverse event(s)
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2 of the genus Betacoronavirus
SoA	Schedule of activities
SUSAR(s)	Suspected, unexpected, serious adverse reaction(s)
TBL	total bilirubin
TEAE(s)	Treatment emergent adverse event(s)
TMF	Trial master file
ULN	Upper limit of normal
US(A)	United States
UV	Ultraviolet
VAS	Visual Analogue Scale
WBC	White blood cells
WHO	World Health Organization

10.11 Appendix 11: Protocol Amendment History

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

10.11.1 Amendment 1

Amendment 1 (22 JUN 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

As of the date of this amendment, three cases of close liver observation (ALT> 3 x ULN (upper limit of norm)), have been reported within the ongoing phase 2 program of BAY1817080, with about 500 patients randomized overall so far. One of these cases was assessed as moderate liver injury seen 4 weeks after start of treatment, with the study drug as most likely cause. The study participant discontinued treatment and recovered from the condition.

Based on this case Bayer has decided to implement testing of liver parameters every two weeks during the treatment period in the ongoing Phase 2 studies as a precautionary measure.

The implementation of the intensified monitoring will ascertain an early identification of potential increases in transaminases and allow for swift initiation of appropriate measures.

Following are the description of change and a brief rationale.

Section # and Name	Description of Change	Brief Rationale
Title page Header throughout the document	Protocol version number is included in the Title page and removed from the header. Date is added in the header.	To reflect the current convention of the company
1.2 Schema 1.3 Schedule of Activities (SoA) 2.3.1 Risk Assessment 10.2 Appendix 2: Clinical Laboratory Tests	3 new visits are added for taking blood samples for liver monitoring (not applicable for participants randomized to active control elagolix) Text updated regarding one case of moderate liver injury Text on blood samples for liver monitoring added.	Testing of liver parameters every two weeks during the treatment period is added as a precautionary measure.
5.2 Exclusion criteria	Addition of extremely low body weight as an example to criterion #7	To support investigator decisions on patient selection in light of the recent liver test results.

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