Official Protocol Title:	A Phase 2a, Proof of Concept, Randomized, Double-blind, Placebo-controlled Clinical Trial, to Evaluate the Efficacy and Safety of MK-7264 in Women with Moderate to Severe Endometriosis-related Pain
NCT number:	NCT03654326
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Title Page

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Protocol Title: A Phase 2a, Proof of Concept, Randomized, Double-blind, Placebo-controlled Clinical Trial, to Evaluate the Efficacy and Safety of MK-7264 in Women with Moderate to Severe Endometriosis-related Pain

Protocol Number: 034-00

Compound Number: MK-7264

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

One Merck Drive

P.O. Box 100

Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

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05-MAY-2018

Sponsor Signatory

Typed Name:
Title:

Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name:
Title:

Date

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2a, Proof of Concept, Randomized, Double-blind, Placebo-controlled Clinical Trial, to Evaluate the Efficacy and Safety of MK-7264 in Women with Moderate to Severe Endometriosis-related Pain

Short Title: MK-7264 Phase 2a in Women with Endometriosis-related Pain

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

In premenopausal female participants between the ages of 18 and 49 years (inclusive) with moderate to severe endometriosis-related pain (ERP [cyclic and non-cyclic]):

Primary Objectives	Primary Endpoints
- To evaluate the efficacy of MK-7264 versus placebo in reducing average daily pelvic pain (cyclic and non-cyclic, combined) during Treatment Cycle 2 (TRC2) as measured by a numeric rating scale (NRS) in the daily eDiary - Hypothesis 1 (H1): MK-7264 is superior to placebo in reducing the average daily pelvic pain score (cyclic and non-cyclic, combined) during TRC2.	- Daily pelvic pain score
- To evaluate the safety and tolerability of MK-7264	- Adverse events (AEs) - Discontinuation of study intervention due to AEs
Secondary Objectives	Secondary Endpoints
- To evaluate the efficacy of MK-7264 versus placebo in reducing average daily cyclic pelvic pain during TRC2 as measured by an NRS in the daily eDiary	- Daily cyclic pelvic pain score
- To evaluate the efficacy of MK-7264 versus placebo in reducing average daily non-cyclic pelvic pain during TRC2 as measured by an NRS in the daily eDiary	- Daily non-cyclic pelvic pain score

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Treatment of moderate to severe ERP
Population	Premenopausal female participants with moderate to severe ERP between the ages of 18 and 49 years (inclusive) will be enrolled in this study.
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind
Masking	Participant Investigator
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 14 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 166 participants will be randomized.

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Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin.	Regimen/ Treatment Period	Use
MK-7264	MK-7264	45 mg	1 tablet bid	oral	Double-blind Treatment Period (Visit 4 up to Visit 6)	Experimental
Placebo	Placebo matching MK-7264	0 mg	1 tablet bid	oral	Double-blind Treatment Period (Visit 4 up to Visit 6)	Placebo

Abbreviations: mg = milligrams; bid = twice a day

Total Number of Arms

2

Duration of Participation

Each participant will participate in the study for approximately 24 weeks from the time the participant signs the Informed Consent Form (ICF) through the final contact. After a screening phase of approximately 8 weeks, each participant will enter a single-blind, placebo run-in phase which consists of 1 menstrual cycle (approximately 4 weeks). Naproxen sodium rescue medication will be provided to participants to use if needed starting at Visit 2. Upon completion of placebo run-in, eligible participants will be randomized to receive assigned double-blind treatment for approximately 8 weeks (ie, 2 menstrual cycles). After the double-blind treatment period, participants will continue in the study for 1 additional menstrual cycle (approximately 4 weeks) during which they will no longer take the study intervention (MK-7264/placebo), but may continue to use rescue medication as needed. During this last post-treatment cycle, a follow-up telephone call will be conducted approximately 14 days after the last dose of the double-blind study intervention.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1. The Data Monitoring Committee for this study is a Standing Internal Data Monitoring Committee (SiDMC).	

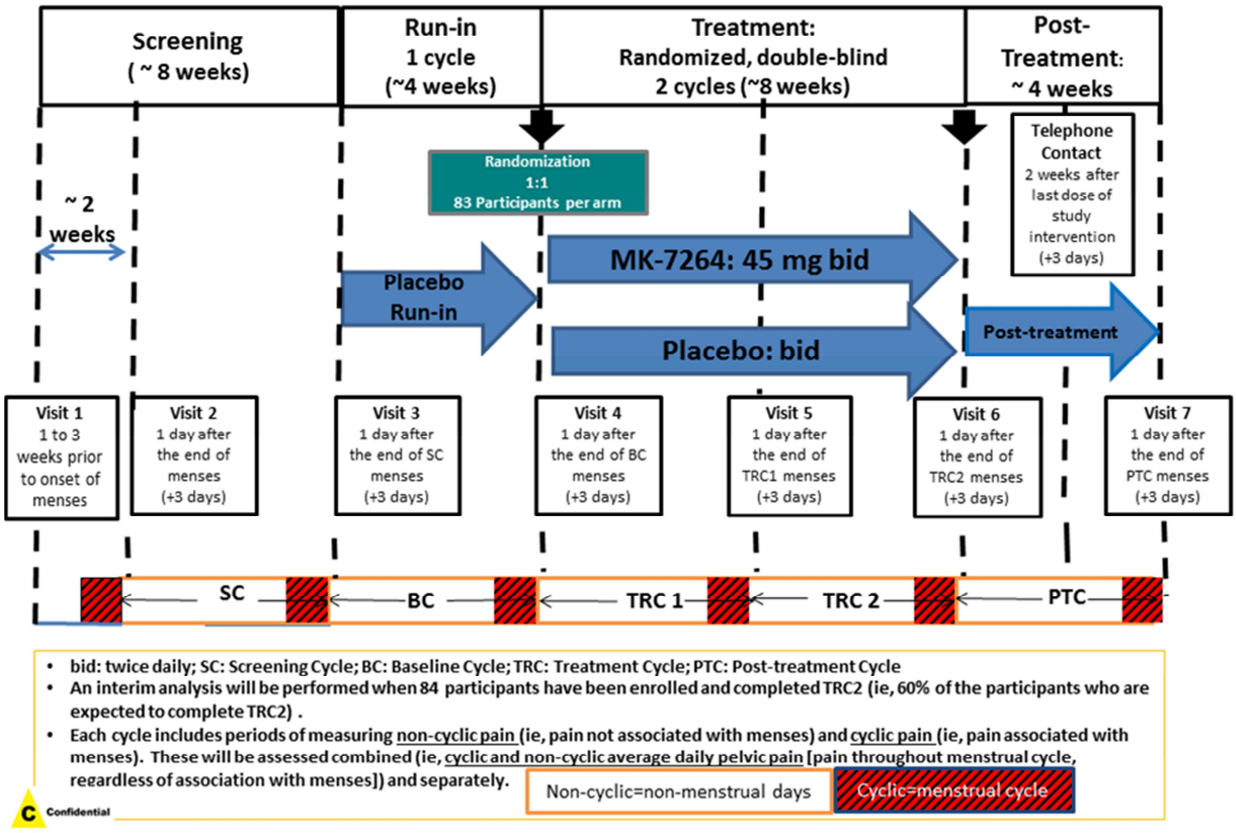
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



1.3 Schedule of Activities (SoA)

Study Period	**Screening**		**Placebo Run-in**	**Treatment Period**			**Post Treatment Period**			**Notes**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Telephone Contact**	**Visit 7**	**DC**	End of menses = end of any visible menstrual flow Asterisk (*) in DC column indicates procedures ***not*** required if DC after V6. See Section 8.10.5 for procedures performed after DC.
Scheduled Day	~1 week before menses	Day after end of menses **Begin SC**	Day after SC menses ends **Begin BC**	Day after BC menses ends **Day1/ Randomization**	Day after TRC1 menses ends	Day after TRC2 menses ends	2 weeks after last dose of study intervention	Day after PTC menses ends		
Scheduling Window	**-14 days**	**+3 days**	**+3 days**	**+3 days**	**+3 days**	**+3 days**	**+3 days**	**+3 days**		
Administrative and General Procedures										
Written Informed Consent	X									Screening may occur over several days after consent is signed.
Informed Consent for Future Biomedical Research (FBR)	X									Participant may participate in main study without participating in FBR.
Assignment of Screening Number	X									
Participant Identification Card	X									At the time of randomization, site will add randomization number to participant identification card
Inclusion/Exclusion Criteria	X	X	X	X						Evaluate entry criteria at each visit, See Section 5.
Medical History	X									
Gynecological History	X									
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	
Rescue Medication (Naproxen sodium) Dispensing and Instructions for Use		X	X	X	X	X				

Study Period	Screening		Placebo Run-in	Treatment Period			Post Treatment Period			Notes
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Telephone Contact**	**Visit 7**	**DC**	End of menses = end of any visible menstrual flow Asterisk (*) in DC column indicates procedures ***not*** required if DC after V6. See Section 8.10.5 for procedures performed after DC.
Rescue Medication (Naproxen sodium) Accountability			X	X	X	X		X	X	
Home Urine Pregnancy Test (UPT) Dispensing		X								If any menstrual cycle is 2 weeks later than expected, participant must perform UPT and contact clinic to schedule visit as soon as possible. Sponsor must be consulted. Additional UPT can be dispensed as needed.
Treatment Randomization				X						
Placebo Dispensing (For Run-In)			X							
MK-7264/Placebo dispensing (For Double-Blind Treatment)				X	X					
MK-7264/placebo accountability				X	X	X			X*	V4: Participant must be ≥80% compliant with placebo run-in to be randomized. After randomization, see Section 6.4 for guidance if study intervention compliance is <80%.
Efficacy Assessments										
eDiary Dispensing; eDiary Instructions		X								
Pelvic Pain Severity NRS		Daily								If Visit 2 is > 1 day after last day of the previous menses, will be completed by participant using eDiary at site during Visit 2 (based on previous day). Also completed on evening of Visit 2 (based on Visit 2 day), and every subsequent evening.
Vaginal bleeding/Non-bleeding Day										
Use of rescue medication (naproxen sodium)										
Use of pain relief medication other than rescue medication provided by the Sponsor										
Impact of Pelvic Pain										
eDiary compliance			X	X	X	X	X	X	X	Participant compliance with daily eDiary entries must be ≥75% to be randomized. See Section 5.1. No compliance checks needed at visits after DC.
EHP-5			X			X			X*	

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Study Period	Screening		Placebo Run-in	Treatment Period			Post Treatment Period			Notes
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Telephone Contact**	**Visit 7**	**DC**	End of menses = end of any visible menstrual flow Asterisk (*) in DC column indicates procedures ***not*** required if DC after V6. See Section 8.10.5 for procedures performed after DC.
PGIC						X			X*	
Collect eDiary								X	X	If participant discontinues study intervention and agrees to be followed, collection of eDiary will occur at last study visit.
Safety Assessments										
Complete Physical Examination	X									
Focused Physical Examination						X			X*	Focused physical exam: cardiovascular system, respiratory system, abdomen/gastrointestinal system, and extremities only.
Height	X									
Weight	X			X		X		X	X	
Calculate Body Mass Index (BMI)	X									
Gynecological Examination	X									Exam includes speculum insertion and bimanual examination.
Breast Examination	X									
Vital Signs (heart rate, blood pressure, temperature)	X		X	X	X	X		X	X	
12-Lead Electrocardiogram	X									
Hematology and Chemistry	X			X		X			X*	
Urinalysis (with microscopy)	X			X		X			X*	Participants with crystals/hematuria will be further evaluated (Section 8.3.8.1).
Urine Pregnancy Test	X	X	X	X	X					If local regulations indicate that urine pregnancy testing should be performed more frequently, follow local regulations where applicable.
Serum Pregnancy Test	X			X		X		X	X	In addition to visits specified, serum pregnancy test also required any time pregnancy is suspected or if urine pregnancy test is positive (unless pregnancy already confirmed by ultrasound).
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	

Study Period	Screening		Placebo Run-in	Treatment Period			Post Treatment Period			Notes
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Telephone Contact**	**Visit 7**	**DC**	End of menses = end of any visible menstrual flow Asterisk (*) in DC column indicates procedures ***not*** required if DC after V6. See Section 8.10.5 for procedures performed after DC.
Pharmacokinetics/Biomarkers										
Pharmacokinetic Sample (blood)				X, X	X	X			X*	Sample Collection Times: V4: pre-dose and 2 hours post-dose V5 and V6: Pre-dose DC: No specified time
Blood for Genetic Analysis				X						If planned genetic analysis is not approved, but FBR is approved and consent is given, sample will be collected for the purpose of FBR. Collected from randomized participants only; see Sections 8.8 and 8.9.
SC=Screening Cycle; BC=Baseline Cycle; TRC1=Treatment Cycle 1; TRC2=Treatment Cycle 2; DC=Discontinuation; NRS=numeric rating scale; eDiary=electronic diary; EHP-5=Endometriosis Health Profile-5; PGIC=Patient Global Impression of Change; V=visit; FBR=future biomedical research; TC=telephone contact; V=visit; UPT=urine pregnancy test										

2 INTRODUCTION

MK-7264, a selective P2X3 receptor antagonist, is being developed for treatment of ERP. It is among the first clinical agents being developed to target this receptor.

The P2X3 receptor is a ligand-gated ion channel primarily expressed on afferent sensory C-fibers which opens in response to extracellular adenosine triphosphate (ATP) released by damaged, stressed, and inflamed tissues [North, R. A. 2004].

P2X3 antagonists have demonstrated benefit in preclinical pain disease models and in ERP (rodent endometriosis/dyspareunia model) [Davenport, A., et al 2017]. MK-7264 was assessed for analgesic and anti-hyperalgesic activity in rodent models of inflammatory, arthritic, and neuropathic pain, and was found to have dose-dependent efficacy for reducing allodynia and hyperalgesia. MK-7264 has previously been evaluated for treatment of refractory chronic cough, interstitial cystitis (IC)/ bladder pain syndrome (BPS), and osteoarthritis (OA) pain.

Eight Phase 2 trials included chronic cough subjects. These completed studies showed that participants who took MK-7264 had reductions in cough frequency and improvements in patient-reported outcomes. The effect of MK-7264 on pain was studied in the IC/BPS and OA trials. Though the primary objective of the OA study was not achieved, trends in pain relief and generally consistent improvements in Patient Global Impression of Change (PGIC), Clinical Global Impression of Change (CGIC), and the Short Form 36 (SF-36) health survey were demonstrated. The IC/BPS study was stopped for operational reasons after the second interim analysis; however, nominally significant improvements in Mean Pain Intensity, Mean Urgency Rating Analysis, Genitourinary Pain Index, and Quality of Life were demonstrated. (Refer to the Investigator’s Brochure [IB] for more information).

Protocol 034 is a proof of concept (PoC) of MK-7264 in participants with moderate to severe ERP.

2.1 Study Rationale

Current medical treatments for ERP are frequently inadequate and have significant safety and tolerability issues that limit their use, often leading patients to surgical treatment. There is a compelling unmet medical need for a new, non-hormonal medical therapy for treatment of ERP, such as an oral P2X3 receptor antagonist, which can avoid the limitations and liabilities of hormonal treatment.

The purpose of this Phase 2a study is to determine the safety and efficacy of MK-7264 in premenopausal women who have moderate to severe ERP. Evaluation of efficacy will be based on average overall, cyclic and non-cyclic pelvic pain scores and use of rescue medication collected using a proprietary electronic Patient Reported Outcome (ePRO). The ePRO instrument for this study will be an electronic diary (eDiary).

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2.2 Background

Refer to the IB for detailed background information on MK-7264.

2.2.1 Pharmaceutical and Therapeutic Background

Endometriosis is an inflammatory, chronic, progressive disease defined by the presence of endometrial glands and stroma outside of the uterus. The condition affects 6-10% of reproductive age women, with worldwide prevalence estimated at approximately 176 million. The pathogenesis is unknown, but leading theories include retrograde menstruation, altered immunity, metaplasia of the germinal epithelium, and metastatic spread [Guidice, L. C. 2010] [Fritz, M. A. 2011].

Approximately 80% of the population with endometriosis suffers from chronic pelvic pain; additionally, ~20% are infertile. Endometriosis-related pelvic pain can be cyclic with menses (dysmenorrhea) and non-cyclic with ovulation, micturition, defecation, intercourse, etc. Approximately 60% of the population has moderate to severe pelvic pain. Endometriosis affects quality of life and interpersonal relationships. It has negative psychological consequences; it is a significant cause of absenteeism; (ie, responsible for more than 10 hours of work loss per week), and results in a substantial economic burden [Guidice, L. C. 2010] [Fuldeore, M. J. 2017] [Parazzini, F., et al 2017].

There is no cure for endometriosis. Hormonal treatments (see below) may delay the progression of the disease (based on laparoscopic findings) but they provide suboptimal pain control. Recurrence of pain requiring additional therapy is common (~30% to 60% of cases) within 6 to 12 months after treatment [Guidice, L. C. 2010].

Pathophysiology

ERP is triggered by many factors, and periodic bleeding accumulation and inflammation are determinant contributors in pathophysiology. Periodic bleeding accumulation from monthly shedding of the ectopic (ie, extra-uterine) endometrium plays a critical role in the pathophysiology of pain, and adhesion and endometrioma formation. In addition, inflammation is mediated by the liberation of pro-inflammatory substances (eg, prostaglandins, interleukins, TNFα, ATP) to excite P2X3 receptors, among others, within the eutopic (ie, within the endometrium) and ectopic endometrial implants. Nerve growth factor is abundantly liberated in the peritoneal micro-environment, generating neuronal migration that produces a higher number of pain-mediating C-fibers, with abundant P2X3 nociceptors. The released ATP acts as a neurotransmitter on P2X3 receptors to relay messages about irritation and inflammation to pain centers in the central nervous system. C-fibers were found in higher proportion and in closer proximity to the peritoneal implant in patients with endometriosis with pain versus patients without pain [Tokushige, N., et al 2006]. P2X3 receptor expression in eutopic and ectopic endometrium of patients with ERP was directly correlated with pain as measured by a visual analog scale [Anaf, V., et al 2002] [Morotti, M., et al 2014] [Ding, S., et al 2017]. Taken together, the data support that ATP and P2X3 receptors both play a key role in neural excitability and pain in patients with ERP and

therefore antagonism of the P2X3 receptor by MK-7264 has the potential to address chronic visceral pain of endometriosis.

ERP Treatment

Scientific societies have proposed guidelines for the treatment of ERP. For empirical therapy (ie, before direct visualization by laparoscopy or laparotomy), combined hormonal contraceptives (CHCs) or progestins, plus nonsteroidal anti-inflammatory drugs (NSAIDs) are generally recommended. Surgery provides confirmation of the diagnosis and treatment of macroscopic disease. In surgically confirmed endometriosis, medical therapy, which may follow inadequate response to surgery, includes a 6-month cycle of a gonadotropin-releasing hormone (GnRH) agonist which provokes a temporary menopausal state. Pain management may require repeated courses of medical therapy and multiple surgical treatments, potentially up until menopause. All hormonal therapies used to treat endometriosis suppress ovulation or inhibit endometrial proliferation, which prevents pregnancy, despite many patients' chief complaint being related to the infertility associated with the disease [Schleedoorn, M. J., et al 2016] [Practice Committee of the American Society for Reproductive Medc 2014] [Dunselman, G. A. J, et al 2014] [Leyland, N., et al 2010].

Efficacy in pain relief is comparable between different hormonal compounds and therefore, the choice of treatment should be based on safety with long-term use, side effect profile and costs [Berlanda, N., et al 2016].

CHCs have been prescribed off-label for decades to treat endometriosis. They have been prescribed cyclically or continuously however, better results have been demonstrated with the continuous (ie, without a hormone-free interval each month) prescription. Contraindications or precautions to the use of CHCs limit their utility in patients with endometriosis harboring other conditions such as migraine, history of thromboembolic disease, liver disease, and smoking in patients >35 years of age. NSAIDs are prescribed despite their efficacy not being demonstrated in well-conducted, randomized clinical trials and the safety concerns associated with chronic use [Taylor, H. S., et al 2017] [Harada, T., et al 2008].

Progestins and injectable GnRH agonists, the only FDA-approved medical treatments for endometriosis, have numerous safety and tolerability issues. Pain control with progestins is due to the inhibition of endometrial growth, antimitotic activity with decidualization, and endometrial atrophy. Progestins (eg, medroxyprogesterone acetate, norethindrone, dienogest, etc.) generally are not indicated for long-term use (ie, greater than 6 to 12 months) and are associated with breakthrough bleeding, weight gain, breast tenderness, mood changes, worsening of the metabolic profile (eg, hypertriglyceridemia) and bone loss [Brown, J. 2014].

GnRH agonists (eg, leuprolide acetate), exert a potent and continuous action on the GnRH receptors, leading to an initial short stimulatory (flare-up) effect on the gonadotropin secretion, followed by a deep depression. GnRH agonists, often administered by depot formulation, induce a profound hypoestrogenic state, amenorrhea and endometrial atrophy, which create tolerability issues, and safety concerns that limit treatment duration. Common

side effects include hot flushes, decreased libido, and vaginal dryness. Bone loss occurs at a rate that is greater than in natural menopause (~1% loss in bone mineral density/month). Use is limited to 6 months when administered alone, or 12 months when combined with 'add-back' hormonal therapy to protect against bone loss [Guidice, L. C. 2010]. Opioids are described only as the last management option in patients with chronic pelvic pain secondary to endometriosis that is refractory to conventional treatment [Martinez, B., et al 2013].

In summary, current medical treatments for ERP provide similar, suboptimal pain control and have safety and tolerability issues that limit their use, often leading patients to surgical treatment. Furthermore, hormonal treatments inhibit fertility in this population of reproductive-age women. Thus, there is a compelling, unmet medical need for a new, non-hormonal medical therapy for treatment of ERP.

2.2.2 Information on Other Study-related Therapy

Naproxen sodium, an NSAID which is commonly used for cyclic pain and has been used as a rescue medication in other studies of endometriosis [Taylor, H. S., et al 2017] will be used as rescue medication in this trial. The dose of naproxen will be according to the local guidance. See Section 6.5.1 for additional details.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

MK-7264 has been evaluated in an extensive nonclinical program. To date, there is little evidence from nonclinical studies that MK-7264 has any direct cellular or direct target organ toxicity.

In the completed and ongoing clinical studies, no major safety concerns have been noted.

Across studies, taste-related AEs were the most frequently reported AEs. The rationale for taste modification exists with P2X2/3 antagonism because of the putative participation of ATP, acting via this receptor, in transducing taste signals from taste bud cells to gustatory afferent pathways. The taste-related AEs are considered mechanism-based, non-serious adverse drug reactions and are expected for MK-7264. To date, they have been fully and rapidly reversible after discontinuation of the drug.

Participants also described oral paresthesia (eg, tingling sensation in the mouth and/or throat). In many instances, participants reported oral paresthesia or hypoesthesia concurrent with taste alterations. Both the taste-related and the oral paresthesia/hypoesthesia AEs are considered mechanism-based, non-serious adverse drug reactions expected for MK-7264.

In pre-clinical studies, crystals of MK-7264 in urine with no evidence of urinary tract injury (eg, microhematuria) were only detected at a dose of 1800 mg bid over 14 days. Repeated measurements of post-void residual volume have not shown any evidence of urinary

retention related to the use of MK-7264. In clinical studies conducted to date in the dose range up to 900 mg bid, there has been no evidence of MK-7264 crystalluria or urolithiasis despite exhaustive clinical, laboratory, and radiographic (in the early clinical studies) safety monitoring. No MK-7264 crystals have been observed in any of the Phase 2 studies.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and ICF documents.

3 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

In premenopausal female participants between the ages of 18 and 49 years (inclusive) with moderate to severe endometriosis-related pain (ERP [cyclic and non-cyclic]):

Objectives	Endpoints
Primary	
• To evaluate the efficacy of MK-7264 versus placebo in reducing average daily pelvic pain (cyclic and non-cyclic, combined) during Treatment Cycle 2 (TRC2) as measured by a numeric rating scale (NRS) in the daily eDiary • Hypothesis 1 (H1): MK-7264 is superior to placebo in reducing the average daily pelvic pain score (cyclic and non-cyclic, combined) during TRC2.	• Daily pelvic pain score
• To evaluate the safety and tolerability of MK-7264	• Adverse events (AEs) • Discontinuation of study intervention due to AEs
Secondary	
• To evaluate the efficacy of MK-7264 versus placebo in reducing average daily cyclic pelvic pain during TRC2 as measured by an NRS in the daily eDiary	• Daily cyclic pelvic pain score
• To evaluate the efficacy of MK-7264 versus placebo in reducing average daily	• Daily non-cyclic pelvic pain score

Objectives	Endpoints
non-cyclic pelvic pain during TRC2 as measured by an NRS in the daily eDiary	
Tertiary/Exploratory	
• To evaluate the average daily use of naproxen sodium rescue medication taken for daily pelvic pain (cyclic and non-cyclic, combined and separately) during TRC2 by number of tablets, compared to the Baseline Cycle (BC)	• Use of naproxen sodium rescue medication for daily pelvic pain

• To evaluate the efficacy of MK-7264 as measured by the proportion of participants with at least 1-point reduction in average daily pelvic pain score (cyclic and non-cyclic, combined and separately) as compared to baseline during TRC2 and
  • Irrespective of analgesic use
  • With no increase in average daily use of rescue medication by number of tablets
  • With no increase in average daily use of rescue medication and no use of concomitant pain medication
  • With no increase in average daily use of rescue medication and no use of concomitant pain medication for ERP
	• Daily pelvic pain score
	• Use of naproxen sodium rescue medication
	• Use of concomitant pain medication

Objectives	Endpoints
• To evaluate the efficacy of MK-7264 versus placebo in reducing average daily pelvic pain (cyclic and non-cyclic, combined and separately) during Treatment Cycle 1 (TRC1) as measured by an NRS in the daily eDiary	• Daily pelvic pain score
• To evaluate average daily pelvic pain (cyclic and non-cyclic, combined and separately) during the Post-treatment Cycle (PTC) after the completion of TRC2, compared to the Screening Cycle (SC)	• Daily pelvic pain scores
• To assess the PGIC rating, the impact scores of pelvic pain and Endometriosis Health Profile-5 (EHP-5) on health-related quality of life during TRC 2	• PGIC ratings • Impact score of pelvic pain • EHP-5
• To evaluate the exposure-response relationship for endometriosis-related pain and taste disturbance	• Plasma exposure of MK-7264 • Daily pelvic pain scores (cyclic and non-cyclic, combined and separately) • Taste-related AEs
• To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.	• Germline genetic variation

4 STUDY DESIGN

4.1 Overall Design

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind, efficacy and safety study of MK-7264 in participants with moderate to severe ERP (cyclic and non-cyclic).

The study will be approximately 24 weeks in duration for each participant, and include 1 menses during screening before Visit 2, followed by 5 complete menstrual cycles, as detailed below:

- One SC during the screening period:
  - Starts at Visit 2, 1 day after the last day of the previous menses

- One BC during the single-blind, placebo run-in period:
  - Starts at Visit 3, 1 day after the last day of the SC menses

- TRC1 and TRC2 after randomization:
  - Start at Visit 4 or 5, 1 day after the last day of the BC or TRC1 menses, respectively.

- One PTC after the participant has stopped taking study intervention (ie, completed TRC2), but may continue to use rescue medication:
  - Starts at Visit 6, 1 day after the last day of TRC2 menses.
  - A telephone contact will occur approximately 14 days after Visit 6.
  - Visit 7 occurs 1 day after the last day of PTC menses

At Visit 2, participants will receive the eDiary which will be used daily through the end of the study to collect pelvic pain score, vaginal bleeding/non-bleeding days, use of naproxen sodium rescue medication, any use of pain relief medication other than the naproxen sodium provided by the Sponsor, and impact of pelvic pain.

This study will use a group sequential design based on prespecified criteria. There will be 1 futility interim analysis (IA). The IA will be conducted when 84 participants have completed TRC2 (ie, 60% of the participants who are expected to complete TRC2). Results of the IA will be reviewed by the Standing Internal Data Monitoring Committee (SiDMC), which will make recommendations to continue or end the study according to the plan described in Section 9 - Statistical Analysis Plan and in a separate SiDMC Charter (see more information in Section 10.1.4.1).

4.2 Scientific Rationale for Study Design

Screening Cycle: Visit 2 to Visit 3

Participants will be dispensed an eDiary and rescue medication at Visit 2 and instructed on their use. The information collected during the SC will allow the investigator to ascertain and verify that the participant meets requirements for study entry (ie, length of menstrual

cycle, average pelvic pain score, compliance with eDiary entries, and compliance with rescue and other pain relief medications) as noted in the Inclusion Criteria (Section 5.1).

Baseline Cycle: Visit 3 to Visit 4/Day 1

At Visit 3, single-blind placebo run-in medication will be dispensed. Thus, in addition to continued monitoring to ensure the participant meets inclusion criteria as noted above, this baseline menstrual cycle has the purpose of familiarizing the participants with the study treatment regimen and excluding participants with a placebo response (ie, participants who have an average pain score during the SC of ≥5, and average pain score during the BC of <5, as measured by the NRS in the Daily eDiary). In addition, participants who are not compliant with the blinded placebo before randomization will be excluded. Baseline measurements for change from baseline analyses will be obtained during this cycle.

Treatment Cycle 1 and 2: Visit 4/Day 1 to Visit 6

TRC1 and TRC2 provide 2 complete menstrual cycles to evaluate the safety and efficacy of MK-7264. Two cycles have been proposed as an adequate timeframe for the efficacy of the medication to be observed. The primary efficacy will be assessed by the change from baseline in average daily pelvic pain score (cyclic and non-cyclic) during TRC2. Efficacy will also be assessed at TRC1 via an exploratory objective.

Post-treatment Cycle: Visit 6 to Visit 7

The purpose of the PTC is to assess the pain scores after participants have stopped double-blind study intervention. Pain scores from the PTC will be compared to pain scores from the SC, as the participants will be under the same clinical circumstances (ie, only rescue medication being used as needed) during both cycles.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The goal of the clinical development program for MK-7264 is to demonstrate its efficacy in the treatment of ERP. The primary efficacy endpoint is the change from baseline in average daily pelvic pain score (cyclic and non-cyclic, combined) during TRC2. For this PoC study, the primary efficacy endpoint addresses daily pelvic pain that represents the most clinically relevant symptom of endometriosis. This endpoint has been published as the primary endpoint in many Phase 2 trials in clinical development programs for endometriosis [Diamond, M. P., et al 2013].

At the end of each day, participants will enter a score in their eDiary rating the worst pelvic pain that they can recall in the past 24 hours, regardless of the use of rescue or other pain relief medication. Pelvic pain severity will be measured using a 0-10 NRS anchored with 0 (no pain) and 10 (extremely severe pain). The average of the daily pelvic pain scores entered in the eDiary will be calculated for each cycle of the study. In addition, each day they will also record any vaginal bleeding, use of rescue medication, use of pain relief medication

other than the naproxen sodium provided by the Sponsor, and impact of pelvic pain. For rescue medication use, the number of tablets taken will be recorded.

The secondary efficacy endpoints evaluate the change from baseline in the average cyclic and non-cyclic pelvic pain scores, separately, during TRC2. Cyclic and non-cyclic pelvic pain during TRC1 and 2 have also been measured in other clinical development programs for endometriosis and provide additional details regarding the timing of the most severe pain. A differential effect in cyclic and non-cyclic pain score is expected due to differences in pathophysiology. The former represents the pathologic event at the eutopic endometrium, involving a higher number of unmyelinated C-fibers, nociceptors, and P2X3 receptors. The latter represents the inflammatory component triggered by the ectopic endometrium over different peritoneal locations (eg, bowel, bladder, Pouch of Douglas, etc.) where multiple proinflammatory substances (prostaglandin, cytokines, ATP, etc.) play a role in pain generation [Howard, F. M. 2009].

The first exploratory endpoint is the average daily use of naproxen sodium rescue medication by number of tablets taken for daily pelvic pain (cyclic and non-cyclic, combined and separately) during TRC2, as compared to the BC. Rescue medication use and the difference in usage between the MK-7264 and placebo treatment groups will be indicators of treatment efficacy in pain control.

The proportion of participants with at least 1-point reduction in average daily pelvic pain score (cyclic and non-cyclic, combined and separately) as compared to baseline during TRC2 is another exploratory endpoint. This endpoint is to evaluate the proportions of participants who have had pain reduction from the study intervention irrespective of analgesic use. However, to further evaluate that pain reduction is not due to use of analgesics, composite endpoints with reduction in pelvic pain and no increased use of rescue medication or other analgesic use will be evaluated. Therefore, the following exploratory endpoints will also be evaluated for this purpose:

- The proportion of participants with at least 1-point reduction in average daily pelvic pain score (cyclic and non-cyclic, combined and separately) as compared to baseline during TRC2, and no increase in average daily use of rescue medication by number of tablets;

- The proportion of participants with at least 1-point reduction in average daily pelvic pain score (cyclic and non-cyclic, combined and separately) as compared to baseline during TRC2, and no increase in average daily use of rescue medication, and no use of concomitant pain medication;

- The proportion of participants with at least 1-point reduction in average daily pelvic pain score (cyclic and non-cyclic, combined and separately) as compared to baseline during TRC2, and no increase in average daily use of rescue medication, and no use of concomitant pain medication for ERP.

While this study is designed to further explore the clinical importance of changes in pelvic pain score, for this PoC study, a 1-point reduction in average daily pelvic pain is the

minimum that will be considered clinically meaningful. Reductions greater than 1-point (ie, 2-point and 3-point reductions) will also be analyzed as part of this objective.

The comparison of pain scores (cyclic and non-cyclic, combined and separately) at PTC versus SC will be used to evaluate the potential change in pain scores after the completion of double-blind study intervention, without the intervention of MK-7264 as in the SC (ie, participants are only exposed to rescue medication).

The PGIC is an exploratory endpoint, to be assessed at the end of TRC2. It is a 7-point scale in the eDiary to collect a participant's rating of overall change in her ERP relative to her condition before initiation of the treatment.

The EHP-5 is an exploratory endpoint to be assessed at baseline and at the end of TRC2. It is an endometriosis-specific questionnaire in the eDiary to assess participant's health-related quality of life at the beginning of the run-in period and at the end of TRC2.

Participants will also answer questions in the eDiary to assess the impact of pelvic pain by determining if their pelvic pain causes any limitations in work/school, physical activities, leisure/social activities, and sleep. Responses to these questions, the EHP-5, and the PGIC will help to determine the effect of pelvic pain on health-related quality of life.

4.2.1.2 Safety Endpoints

The safety data for MK-7264 to date has been described in detail in Section 2.3 and in the IB.

In support of the safety objective to evaluate the safety and tolerability profile of MK-7264, the safety and tolerability endpoints will be assessed by clinical evaluation of AEs (including taste-related AEs as Tier 1 events) and inspection of other study parameters including vital signs, physical examination, and standard laboratory safety tests at time points specified in the SoA. AEs are graded and recorded according to Section 8.4.

4.2.1.3 Pharmacokinetic Endpoints

The relationship between MK-7264 plasma concentrations/exposure and pelvic pain score (cyclic, non-cyclic, combined and separately)/side effects will be explored. Exploratory population pharmacokinetic (PK) analyses will be conducted to understand the exposure-response relationships between MK-7264 and efficacy and safety data.

4.2.1.4 Pharmacodynamic Endpoints

No pharmacodynamics biomarkers are planned for this study.

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants

that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to the study intervention(s), the disease under study, and related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).

DNA samples will be analyzed for variation across the entire genome. Analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

4.2.1.6 Future Biomedical Research

The Sponsor will conduct future biomedical research on DNA specimens for which consent was provided during this clinical study.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of this future biomedical research substudy are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

A placebo group is included in this study to maintain the study blinding, allowing for an unbiased assessment of efficacy and safety. Participants may discontinue the study intervention at any time. Since naproxen sodium rescue medication will be provided, the use of a placebo is justified.

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

The dose of MK-7264 will be 45 mg bid throughout the study. See Section 4.3.3.

4.3.2 Maximum Dose/Exposure for This Study

The maximum dose will be 45 mg bid. Participants will be exposed to MK-7264 for approximately 8 weeks. For more information, see Section 6 - Study Intervention and Section 4.3.3.

4.3.3 Rationale for Dose Interval and Study Design

Of the indications studied, the clinical development of MK-7264 has progressed the furthest for the chronic cough indication. In Protocol 010, a Phase 2, crossover, dose escalation study in refractory chronic cough, 7 doses were evaluated (7.5, 15, 30, 50, 100, 150, and 200 mg bid). After 4 days of treatment, participants in the 30 and 50 mg bid dose groups experienced a near maximal, statistically significant reduction in cough. Taste disturbances (ie, ageusia, dysgeusia, and hypogeusia), which are common side effects, were less frequent at doses <50 mg bid.

The largest and longest phase 2 study completed to date was Protocol 012, in participants with chronic cough. It was a 12-week, parallel design, 4-arm study (placebo and MK-7264 at 7.5, 20, or 50 mg bid), with 253 participants enrolled. A statistically significant reduction in the primary endpoint (mean change from baseline in objective awake coughs per hour at Week 12) relative to placebo was observed for the 50-mg bid dose. Taste disturbances, the most common AEs reported, were dose related: 10% at 7.5 mg, 49% at 20 mg, and 81% at 50 mg bid. At the 50 mg bid dose, 10% of participants discontinued treatment due to altered taste effect AEs.

These results suggest a relatively close association between dose/exposure, efficacy (ie, cough rate reduction) and taste disturbances. Based on these results, an exposure-response model was developed to support the dose selection for the Phase 3 studies of MK-7264 for chronic cough with an aim to select doses which maximize the efficacy (high dose) and minimize the taste disturbance (low dose). According to this model, the AUC50 (area under the curve required to achieve 50% of the maximal response) was 721 ng.hr/mL, which would result from a dose of 10 mg. Considering a 2-3 fold higher dose is required to achieve a maximum cough suppression response, a dose of 30 mg is expected to provide a near maximal response (29% reduction in cough rate, placebo adjusted). The model based simulations also indicated that an increase in the dose from 30 mg to 45 mg would result in an additional 2.2% reduction in cough frequency and a 9.6% increase in taste disturbance incidence rate (ie, from 57.4% to 67%).

To select the dose for treatment of ERP, previous exposure–response (cough rate reduction and taste disturbance) experience was leveraged, keeping in mind that increasing the dose of MK-7264 will increase the likelihood for higher incidence of taste disturbance, which could lead to participant non-acceptance, noncompliance and study drop-out. The dose selected for the current study was based on the assumption of similarity of the P2X3-related mechanism of action for pain and for cough and similar exposure-response between cough and pain, as well as to mitigate potential rightward shift of exposure-response for pain relative to cough (ie, potential that ERP is less sensitive than cough reflex). Thus, to assess the efficacy of MK-7264 for the treatment of ERP, a dose of 45 mg bid was selected.

The appropriateness of this dose is also supported by preclinical data. The concentration range (170-793 ng/mL) that was found to be efficacious in preclinical models for neuropathic, arthritic and inflammatory conditions brackets the steady state Cmax following 45 mg bid (569 ng/mL). Additionally, the Cmax values are expected to be ~3.5-fold above the Ki value for P2X3 after accounting for protein binding and plasma to tissue partition.

Taken together, data from preclinical in vitro and animal studies and human experience in pain (OA of the knee and IC/BPS [reference the IB for additional information]) and cough, including dropout rates and taste tolerability, support the selection of the 45 mg bid dose for the current study.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

Early study termination will be the result of the following specified criteria:

One formal IA will be conducted when 84 participants (ie, 60% of the participants who are expected to complete TRC2) have completed TRC2. Results of the IA will be reviewed by the SiDMC, which will make recommendations to continue or end the study according to the plan described in Section 9 - Statistical Analysis Plan.

5 STUDY POPULATION

Female participants with moderate to severe endometriosis-related pelvic pain (cyclic and non-cyclic) between the ages of 18 and 49 years (inclusive) will be enrolled in this study.

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

5.1 Inclusion Criteria

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

1. Participant has been surgically (laparoscopy or laparotomy) diagnosed with endometriosis within 10 years of study entry as documented by medical records.

2. Participant has cyclic (secondary dysmenorrhea) AND non-cyclic, moderate to severe endometriosis-related pelvic pain, as confirmed by an overall score of ≥5 at Visit 1 based on the participant's last 2 menstrual cycles using an NRS (0-10 anchored with 0 [no pain] and 10 [extremely severe pain]).

3. Participant has had spontaneous, (ie, without hormonal therapy) regular, menstrual cycles with a cycle length between 24 to 38 days (inclusive) for the past 2 months before Visit 1.

Demographics

4. Participant is a female.

5. Participant is from 18 years to 49 years of age inclusive, at the time of signing the informed consent.

6. Participant's body mass index (BMI) is between 18 kg/m^2 to 40 kg/m^2 inclusive, at Visit 1.

Female Participants

7. Participant is not pregnant, not breastfeeding, and the following condition applies:

   The participant agrees to follow the contraceptive guidance in Appendix 5 from the time of signing informed consent through the last day of the post-treatment cycle of the study (Visit 7) or for at least 14 days after the last dose of double blind study intervention if the participant discontinues study intervention.

Informed Consent

8. The participant (or legally acceptable representative, if applicable) provides written informed consent for the study. Participant must be willing and able to comply with all aspects of the protocol, including the use of the eDiary, to the satisfaction of the investigator/qualified designee before randomization. The participant may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Study Participation

9. Participant must agree to switch from her usual analgesic medication to only that which is permitted in the study (ie, naproxen sodium rescue medication provided by the Sponsor).

At Visit 3 (Before Placebo Run-in)

10. Participant's menstrual cycle before Visit 3 (SC) was 24 to 38 days (inclusive) as documented in the eDiary.

11. Participant reports at least moderate pelvic pain during the SC as defined by average daily pelvic pain (cyclic and non-cyclic) score ≥5.

    Note: Pain severity score will be measured using 0-10 NRS anchored with 0 (no pain) and 10 (extremely severe pain).

12. Participant has demonstrated compliance with ≥75% of daily eDiary entries (ie, pelvic pain score, vaginal bleeding, rescue medication intake, intake of pain relief medication other than naproxen sodium provided by Sponsor, and impact of pelvic pain) during the SC.

    Note: eDiary compliance will be automatically calculated by the eDiary vendor partner and a report will be provided. The investigational site should review the report before the participant's scheduled visit to assess eligibility.

13. Participant has taken only the study provided rescue medication, at a dose not exceeding the maximum dose determined by the investigator according to the local label, for control of ERP during the SC as evidenced in the eDiary.

    Note: Short term use (ie, ≤3 days) of other non-opioid pain medications for acute conditions other than ERP is permitted.

At Visit 4 (Before Randomization)

14. Participant's menstrual cycle before Visit 4 (BC) was 24 to 38 days (inclusive) as documented in the eDiary.

15. Participant reports at least moderate pelvic pain during the BC as defined by average daily pelvic pain (cyclic and non-cyclic) score ≥5.

    Note: Pain severity score will be measured using 0-10 NRS anchored with 0 (no pain) and 10 (extremely severe pain).

16. Participant has demonstrated compliance with ≥75% of daily eDiary entries (ie, pelvic pain score, vaginal bleeding, rescue medication intake, intake of pain relief medication other than naproxen sodium provided by Sponsor, and impact of pelvic pain) during the BC.

    Note: eDiary compliance will be automatically calculated by the eDiary vendor partner and a report will be provided. The investigational site should review the report before the participant's scheduled visit to assess eligibility.

17. Participant is ≥80% compliant with the placebo run-in medication (as determined by site-performed tablet count).

18. Participant has taken only the study provided rescue medication, at a dose not exceeding the maximum dose determined by the investigator according to the local label, for control of endometriosis-related pelvic pain during the BC as evidenced in the eDiary.

    Note: Short term use (ie, ≤3 days) of other non-opioid pain medications for acute conditions other than ERP is permitted.

5.2 Exclusion Criteria

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

Medical Conditions

1. Participant had no pelvic pain for more than 50% of the days in her last menstrual cycle according to the participant's recollection.

2. Participant has a surgical history of hysterectomy and/or bilateral oophorectomy.

   Note: Participants who have undergone surgical sterilization (eg, bilateral salpingectomy, tubal ligation) are permitted in the trial.

3. Participant had undiagnosed (unexplained), abnormal, vaginal bleeding within the past 6 months before screening.

4. Participant has chronic pelvic pain not caused by endometriosis that requires chronic analgesic or other chronic therapy (including, but not limited to, pain caused by IC, BPS, adenomyosis [as confirmed by imaging], symptomatic uterine fibroids, irritable bowel syndrome, vulvodynia, or hysteroscopic sterilization).

5. Participant has chronic, non-pelvic pain not caused by endometriosis that requires chronic analgesic or other chronic therapy (including, but not limited to, fibromyalgia, chronic back pain or chronic headaches).

6. Participant has a clinically significant gynecologic condition identified in the screening evaluation including, but not limited to, endometriomas of any size, persistent (present longer than 4 months) complex ovarian cysts larger than 3 cm, simple ovarian cysts larger than 5 cm, or an active sexually transmitted disease. Participants may be rescreened after completing treatment for infection or for simple ovarian cysts.

7. Participant plans to schedule elective surgery during the study execution or had surgery in the past 6 months before screening that continues to require pain management.

8. Participant has a history of anaphylaxis or cutaneous adverse drug reaction (with or without systemic symptoms) to sulfonamide antibiotics or other sulfonamide-containing drugs. (Note: MK-7264 contains a sulfonamide moiety.)

9. Participant has a known allergy/sensitivity or contraindication to MK-7264 or its excipients (Note: refer to the IB for details regarding excipients of MK-7264).

10. Participant has an allergy/sensitivity/intolerance to naproxen sodium (rescue medication) or any contraindication to its use, or has experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs.

    Note: Proton pump inhibitors (PPIs) may be used per investigator discretion as needed.

11. Participant has an estimated glomerular filtration rate <50 mL/min/1.73 m^2 (using the Chronic Kidney Disease Epidemiology Collaboration [CKD EPI] formula) at Visit 1.

12. Participant has systolic blood pressure >160 mm Hg or diastolic blood pressure >90 mm Hg at Visit 1.

13. Participant is, at the time of signing informed consent, a user of recreational or illicit drugs or has had a recent history (within the last year) of drug or alcohol abuse or dependence, per the investigator's discretion. Participants are asked to follow the protocol-specified restrictions on alcohol use during the study (Section 5.3.1).

14. Participant has a history of ERP that was non-responsive to treatment with CHCs, GnRH antagonists, GnRH agonists, progestins, or aromatase inhibitors.

    Note: Participants who achieved a partial response or were treatment failures due to side effects should not be excluded.

15. Participant has a history of malignancy ≤5 years before signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.

16. Participant has donated or lost ≥1 unit of blood (approximately 300 mL) within 8 weeks before the first dose of MK-7264.

17. Participant has a positive urine pregnancy test at any time before randomization. If the urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Prior/Concomitant Therapy

18. Participant has required more than 2 weeks of continuous use of narcotics for treatment of ERP within 6 months of Visit 1.

19. Participant has received any treatment listed in Table 1 more recently than the "Last Allowable Use" as indicated in the table, or must continue to receive any treatment listed in Table 1 during the study.

Table 1 Prohibited Medications and Other Substances

Prohibited Medications[1]: Hormones	**Last Allowable Use**
GnRH agonists with 1-month duration or GnRH antagonists, aromatase inhibitors, menotropins and human chorionic gonadotropin (hCG)	3 months before Visit 1
Injectable GnRH agonist with 3-month duration (eg, leuprolide)	10 months before Visit 1
Oral, patch, and implanted contraceptives; vaginal ring, and medicated intrauterine device (IUD); oral progestins (eg, norethindrone acetate and dienogest)	2 months before Visit 1[2]
Injectable hormonal contraception with 1-month duration	3 months before Visit 1
Injectable hormonal contraception with 2-month duration	6 months before Visit 1
Injectable hormonal contraception with 3-month duration; injectable medroxyprogesterone acetate; injectable depomedroxyprogesterone acetate	9 months before Visit 1
IUD (non-hormonal)	Before Visit 1[3]
Prohibited Medications[1]: Analgesics	**Last Allowable Use**
• NSAIDs (eg, aspirin, ketorolac) o Protocol-specified naproxen sodium rescue medication is permitted. • COX-2 inhibitors • Other non-specified analgesics (eg, acetaminophen or paracetamol)	At Visit 2[4]
• Opioid analgesics (eg, tramadol and tapentadol)	5 days before Visit 2
Prohibited Medications[1]: Other	**Last Allowable Use**
• Herbal remedies containing Hypericum perforatum (eg, Kava kava and St. John's wort)	At Visit 1
• Glucocorticoids (oral or intravenous) • Anti-Tumor Necrosis Factor (TNF)/Anti-Nerve Growth Factor (NGF)	2 months before Visit 1

[1]Excluded from the time point specified above and throughout the study.
[2]Not including emergency contraceptive pills.
[3]Intrauterine device (non-hormonal) must be removed before the day of screening visit.
[4]Short term use (ie, ≤3 days) of non-opioid pain medications for acute conditions (other than ERP) is permitted.

Prior/Concurrent Clinical Study Experience

20. Participant has received MK-7264 in a previous clinical study.

21. Participant is currently participating in or has participated in an interventional clinical study with an investigational compound or device within 30 days of participating in the current study.

Diagnostic Assessments

22. Participant has clinically significantly abnormal laboratory tests at Screening, including:

    a. Alkaline phosphatase (AP), alanine aminotransferase (ALT, SGPT), aspartate aminotransferase (AST, SGOT) >200% of the upper limit of normal, or total bilirubin >150% of the upper limit of normal.

    b. Hemoglobin <10 gm/dL, white blood cell count <2500 mm^3, neutrophil count <1500 mm^3, platelet count <100 × $10^3/mm^3$.

Other Exclusions

23. Participant has other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator or Sponsor, would make the participant inappropriate for entry into this study.

24. Participant is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

5.3.1 Caffeine, Alcohol, and Tobacco Restrictions

Based on the known metabolism of MK-7264, there are no effects of alcohol, caffeine, or tobacco associated with the study treatment.

However, during the study, participants are asked to refrain from consuming more than 3 alcoholic beverages or equivalent (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day.

5.3.2 Activity Restrictions

No activity restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. 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 any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

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

Clinical supplies [study intervention(s) provided by the Sponsor] will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 2.

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Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
Placebo	Other	Placebo Matching MK-7264	Other	Tablet	0 mg	1 tablet bid	Oral	Visits 3 to 4 (Run-in Period)	Placebo	IMP	Provided centrally by the Sponsor
MK-7264	Experimental	MK-7264	Drug	Tablet	45 mg	1 tablet bid	Oral	Visits 4 to 6 (Treatment Period)	Experimental	IMP	Provided centrally by the Sponsor
Placebo	Placebo Comparator	Placebo Matching MK-7264	Other	Tablet	0 mg	1 tablet bid	Oral	Visits 4 to 6 (Treatment Period)	Placebo	IMP	Provided centrally by the Sponsor
Rescue Medication for both Treatment Arms	Other	Naproxen sodium	Drug	Tablet	275 mg	Per local guidance	Oral	Visits 2 to 7 (Screening, Run-in, Treatment and Post-treatment Periods)	Rescue Medication	NIMP	Provided centrally by the Sponsor

All supplies indicated in Table 2 will be provided per the "Sourcing" row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number.

Refer to Section 8.1.13 for details regarding administration of the study intervention.

6.1.1 Medical Devices

Medical devices are not used in this study.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

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

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Treatment allocation/randomization will occur centrally using an interactive response technology (IRT) system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to MK-7264 study intervention and placebo study intervention, respectively.

6.3.2 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

- Severity of pelvic pain
  - Moderate (ie, average score of ≥5 to <8 on the NRS in the eDiary during the BC), or
  - Severe (ie, average score of ≥8 on the NRS in the eDiary during the BC)

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. MK-7264 and matching placebo will be packaged identically so that blind is maintained. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the group assignments.

See Section 8.1.15 for a description of the method of unblinding a participant during the study should such action be warranted.

6.4 Study Intervention Compliance

Records of treatment compliance for each participant will be kept during the study. Compliance will be based on tablet count. In cases in which tablet count cannot be performed, participant reporting will be used to assess compliance. Issues with compliance should be discussed with the participant and addressed as deemed appropriate by the investigator.

Interruptions from the protocol specified treatment plan in which a participant's compliance is <80% require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Sponsor consultation and written documentation of collaborative decision on participant management is not required if reason for <80% compliance is due to an AE. Such instances of <80% compliance will not be considered a protocol deviation. Consultation should occur in a timely manner upon site learning of poor study intervention compliance. While awaiting Sponsor feedback, the investigational site should conduct participant counseling regarding importance of study intervention adherence, and the investigator can dispense study

intervention after such counseling, if in their medical judgment, the participant is able to comply moving forward with study intervention instructions.

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed from the time specified for each medication in Table 1 (Section 5.2) until early discontinuation or end of the post-treatment period. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

6.5.1 Rescue Medications and Supportive Care

Naproxen sodium 275 mg tablets will be provided to participants for use as rescue medication for ERP from Visit 2 until early discontinuation or last study visit. Since the maximum appropriate dose varies by region, the dose of naproxen sodium will be based on investigational site's recommendation and the local guidance.

Participants will be instructed that they should not take pain medications other than site dispensed naproxen sodium for ERP during the study, and that naproxen sodium is to be used only as a rescue medication for ERP, not prophylactically or routinely.

The naproxen sodium tablets provided as rescue medication should not be used for the treatment of conditions other than ERP during the study. Participants must return all remaining naproxen sodium at each study visit, or discontinuation visit.

Note: Short term use (ie, ≤3 days) of other non-opioid pain medications for acute conditions (other than ERP) is permitted. However, the investigator should caution the participants on the use of other NSAIDs on the same day that the participant uses the naproxen sodium rescue medication.

6.6 Dose Modification

Participants will be randomized to a fixed dose regimen of MK-7264, 45 mg bid or matching placebo for the duration of the study.

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study. Participants should be advised to return to the care of their primary physician and/or obstetrician/gynecologist.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.15). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic intervention allocation/randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.10.5.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.10.5.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.

- The participant's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.

- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk from continued administration of study intervention (including recommendation to discontinue participant from study treatment as part of monitoring for crystalluria/urolithiasis, see Section 8.3.8.1–Renal and Urological Safety Procedures).

- The participant has a confirmed positive serum pregnancy test.

- In case of clinically significant and potentially drug-related rash or signs and/or symptoms consistent with allergic drug reaction or anaphylaxis to study treatment.

For participants who are discontinued from study intervention but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed. Section 8.10.5 describes the procedures to be completed at each specified visit.

Discontinuation from study intervention is "permanent." Once a participant is discontinued, he/she shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.14. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

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

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Study File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- 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.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will be approximately 62.5 mL.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or future biomedical research. If there are changes to the participant's status during the study (eg, health or age of

majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

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

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

Specifics about a study and the study population will be added to the consent form template at the protocol level.

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the future biomedical research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the future biomedical research substudy. A copy of the informed consent will be given to the participant.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator who is a qualified physician to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent. At the time of intervention

allocation/randomization, site personnel will add the intervention/randomization number to the participant identification card.

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee (refer to electronic case report form [eCRF] entry guidelines).

8.1.5 Gynecological History

A gynecological history (including menstrual history) will be obtained by the investigator or qualified designee for all participants. Special attention should be given to the gynecologic-related inclusion and exclusion criteria (eg, surgical confirmation of endometriosis, history of pelvic pain, characteristics of participant's menstrual cycle, previous gynecologic surgery, etc.). See Section 5.

As part of the gynecological history and to ensure the participant is eligible for study participation, the investigator or qualified designee will confirm that the participant has cyclic (secondary dysmenorrhea) AND non-cyclic, moderate to severe endometriosis-related pelvic pain, using an NRS (0-10 anchored with 0 [no pain] and 10 [extremely severe pain]). The participant's rating of her pain during her last 2 menstrual cycles must be an overall score of ≥5 to be eligible for participation in the study.

Pregnancy history (including gravidity and parity), including number of previous pregnancies and number of live births should be collected for all subjects at Visit 1 and reported on the appropriate eCRF.

8.1.6 Prior and Concomitant Medications Review

8.1.6.1 Prior Medications

The investigator or qualified designee will review prior medication use and record prior medication taken by the participant before screening. See Section 6.5 – Concomitant Therapy and refer to eCRF entry guidelines.

8.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

8.1.7 Rescue Medication (Naproxen Sodium) Dispensing and Instructions for Use

Naproxen sodium rescue medication (275 mg tablets) will be dispensed to each participant at Visits 2 through 6, inclusive. The investigator or qualified designee will instruct the participant on the proper use of the rescue medication according to local guidance.

Participants should be reminded that they should not take additional pain medication for ERP and that the naproxen sodium tablets provided by the Sponsor should be used only for ERP and not for other ailments during the course of the study.

Overdoses must be reported to the Sponsor (See Sections 8.5 and 10.3.1).

8.1.8 Rescue Medication Accountability

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

8.1.9 Home Pregnancy Test Dispensing

Starting at Visit 2, participants will be given a urine pregnancy test (UPT) to take home. Additional UPTs for home use will be dispensed to participants as needed.

8.1.10 Assignment of Screening Number

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

Any participant who is screened more than once will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 8.10.1.

8.1.11 Placebo Dispensing (for Run-In Period)

All participants will be dispensed single-blind, placebo run-in medication.

8.1.12 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.13 Study Intervention Administration

The distribution of study intervention will be witnessed by the investigator and/or qualified designee at the study visits. Participants will receive either MK-7264 45 mg or placebo matched to 45 mg MK-7264. Participants should be instructed to take 1 tablet from the bottle bid.

Participants will be provided with enough study intervention to last between study site visits.

Study intervention should begin on the day of treatment randomization and will be administered at the study site at Visit 4. This first dose of study treatment at Visit 4 should be administered after the pre-dose PK sample collection and before approximately 11:00 AM. As dosing is bid, the next dose should be taken orally in the evening, approximately 12 hours later. Subsequent dosing will be performed by the participant (ie, unsupervised at her home) bid, approximately 12 hours apart at approximately the same time each day. However, on the day of a study site visit, the morning dose should not be taken at home and instead will be given as a witnessed dose at the study site after the pre-dose PK sample collection, and before approximately 11:00 AM. Participants should be contacted (eg, by phone or text) and reminded not to take their study intervention before a study site visit that includes pre-dose PK collection.

Participants who vomit after dosing or miss a dose should be instructed to continue with the next scheduled dose.

8.1.13.1 Timing of Dose Administration

Study intervention (ie, MK-7264 or matching placebo) will be administered orally, bid, approximately 12 hours apart for approximately 8 weeks (ie, two menstrual cycles) during the double-blind study treatment period.

8.1.14 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the study, all applicable activities scheduled for the Discontinuation visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4 .

8.1.14.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the

Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.15 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the drug used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's treatment assignment, the investigator or who is a qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this study, the IRT

system should be used for emergency unblinding in the event that this is required for participant safety.

At the end of the study, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

8.1.16 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

8.2.1 Electronic Patient-reported Outcomes

8.2.1.1 eDiary Dispensing and Instructions

At Visit 2, each participant will be given a handheld electronic device containing the eDiary and will be properly trained and instructed on its use by the investigator or qualified designee. Participants should bring their eDiary device for all study visits, and should be contacted and reminded to do so (eg, by phone or text) before each visit.

Participants will be instructed to enter the *daily* eDiary information described below (Sections 8.2.1.2 through 8.2.1.6) on the evening of Visit 2, and every evening through study end. Preferably, this will be done at the same time each day (eg, before bedtime). Participants will be instructed to think only about the past 24 hours when completing the daily questions. If a participant forgets to enter the daily information, she will have 24 hours to do so.

Participants will also be asked to complete the daily eDiary entries from the previous day during Visit 2 (ie, while at the study site), if Visit 2 occurs more than one day after the last day of the previous menstrual bleeding.

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

Completion of the daily questions in the eDiary is expected to take less than 10 minutes.

Participants will be instructed to complete the EHP-5 and PGIC (Sections 8.2.1.7 and 8.2.1.8) at the same time they complete their daily eDiary entries on the evenings of the visits indicated on the SoA. If these are forgotten, the participant will have 48 hours to complete them starting from the time when the visit is logged in to the eDiary.

Additional information for the site staff can be found on a secure online portal. Additional information for the participants can be found within the eDiary.

8.2.1.2 Pelvic Pain Severity Numeric Rating Scale

At the end of every day (just before she goes to bed), the participant will enter in her eDiary a rating of her worst pain or cramps in her pelvic area in the past 24 hours. This will be measured using a 0-10 NRS anchored with 0 (no pain or cramps) and 10 (extreme pain or cramps).

In order to confirm participant eligibility at Visit 3 and 4, study site staff will confirm that the participant has reported at least moderate pelvic pain during the SC and the BC as defined by average daily pelvic pain (cyclic and non-cyclic) score $\geq$5.

8.2.1.3 Vaginal Bleeding or Non-bleeding Days

At the end of every day (just before she goes to bed), the participant will enter in the eDiary whether or not she had any vaginal bleeding during the past 24 hours and the amount of bleeding (eg, spotting, light, moderate, or heavy).

In order to confirm participant eligibility at Visit 3 and 4, study site staff will confirm that the participant's menstrual cycles before Visit 3 (SC) and Visit 4 (BC) were 24 to 38 days (inclusive) as documented in the eDiary.

8.2.1.4 Use of Rescue Medication (Naproxen sodium)

At the end of every day (just before she goes to bed), the participant will enter in the eDiary whether or not she took any of the pain relief tablets (naproxen sodium) provided by the study site in the last 24 hours. If yes, she will provide the number of tablets taken and the reason for taking them.

8.2.1.5 Use of Pain Relief Medication Other than Rescue Medication

At the end of every day (just before she goes to bed), the participant will enter in the eDiary whether or not she took any other pain relief medication (ie, other than the naproxen sodium provided by the study site) in the last 24 hours. If yes, she will provide the medication name (selected from a dropdown menu), dose, when taken, and the reason taken (ie, for ERP, other reasons, or ERP and other reasons).

In order to confirm participant eligibility at Visit 3 and 4, study site staff will confirm that the participant has taken only the study provided rescue medication for control of ERP during the SC and BC as evidenced in the eDiary. (Short term use (ie, $\leq$3 days) of other non-opioid pain medications for acute conditions other than ERP is permitted.)

8.2.1.6 Impact of Pelvic Pain

At the end of every day (just before she goes to bed), the participant will answer questions in the eDiary to assess the impact, if any, of pain or cramps in her pelvic area on the following items: limitations in paid work/work around the home/school work, limitations in physical activities, limitations in leisure or social activities and limitations on sleep.

8.2.1.7 Endometriosis Health Profile-5

The EHP-5 is an endometriosis-specific questionnaire to assess the participant's health-related quality of life at the beginning of the run-in period and at the end of TRC2.

Participants will complete the EHP-5 in the eDiary at approximately the same time in the evening as other eDiary entries on the day of the visits outlined in the SoA. The recall period on the EHP-5 is 'the last 4 weeks'. It is anticipated to take less than 5 minutes to complete.

8.2.1.8 Patient Global Impression of Change

The PGIC is a 7-point scale collecting a participant's rating of overall change in her ERP relative to her condition before initiation of the treatment.

At the end of TRC2, participants will complete the PGIC in the eDiary. The PGIC should be completed at approximately the same time in the evening as other eDiary entries on the day of the visit outlined in the SoA. It is anticipated to take less than 5 minutes to complete.

8.2.2 eDiary Compliance

Daily eDiary entries will be uploaded automatically into a secure online portal managed by the eDiary vendor. Sites will have access to reports within an automated database compiled from uploaded eDiary data which will be used to identify non-compliant subjects. Sites will not be able to view subject eDiary responses directly to prevent unblinding of site personnel.

Sites will monitor participant compliance in completing the following daily eDiary entries:

- Pelvic pain score,
- Vaginal bleeding,
- Rescue medication intake,
- Intake of pain relief medication other than the naproxen sodium provided by the Sponsor, and
- Impact of pelvic pain.

Participants must respond to each one of the daily eDiary questions in order to be considered compliant for a given day. Sites will review the compliance reports regularly and before every in clinic or telephone visit after Visit 2 to identify participants who have been non-compliant with the protocol. Participants who have been non-compliant with eDiary entry for 1 day should be contacted immediately. In order to confirm participant eligibility at Visit 3 and 4, study site staff will confirm that the participant has demonstrated compliance with ≥75% of daily eDiary entries (Section 5.1).

Additionally, participants should be contacted any time that the reports indicate that the participant has used pain relief medication other than the rescue medication.

Sites are not required to continue to monitor eDiary compliance after a participant has discontinued study intervention.

The site is expected to make every reasonable effort to contact the participant (repeated calls, emails, text messages, etc.) to provide appropriate counseling. Site personnel must document any contact or attempted contact on a Subject Contact Log to be maintained at the site. Supplemental study visits may be scheduled for subject re-training.

8.2.3 Collect eDiary

The eDiary will be collected from the participant at her last study visit. Additional details will be provided in a separate document.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn over the course of the study (from prestudy to poststudy visits) can be found in Section 8.

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

8.3.1 Complete Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. At a minimum, the examination will include assessments of the following: general appearance; skin and lymphatic; eyes, ears, nose, throat; cardiovascular system; respiratory system; abdomen/gastrointestinal system; urological system; musculoskeletal and neurological systems. Other body systems may be examined. Height (cm) and weight (kg) will also be measured and recorded.

A brief focused physical exam may be performed at any study site visit that does not already include a physical exam if deemed necessary by the investigator due to signs/symptoms. A physical exam (complete or focused) can be performed at any unscheduled visit if deemed necessary by the investigator.

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

8.3.2 Focused Physical Examinations

A brief focused physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. At a minimum, the examination will include assessments of the following: cardiovascular system,

respiratory system, abdomen/gastrointestinal system, and extremities. Other body systems may be examined.

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

8.3.3 Calculate Body Mass Index

BMI will be calculated (weight/height^2 in kg/m^2) by the investigator or qualified designee based on participant's height and weight at Visit 1 to ensure the participant meets study Inclusion Criteria (see Section 5.1).

8.3.4 Gynecological Examination

A gynecological examination will be conducted by an investigator or medically qualified designee (consistent with local requirements). The examination will include speculum insertion and a bimanual examination. Only abnormal findings should be recorded on eCRFs, either as medical history or AEs.

8.3.5 Breast Examination

A breast examination will be conducted by an investigator or medically qualified designee (consistent with local requirements). Only abnormal findings should be recorded on eCRFs, either as medical history or AEs.

8.3.6 Vital Signs

Vital signs will be measured in a sitting position after 5 minutes rest and will include oral or tympanic temperature (in centigrade), systolic and diastolic blood pressure (mm Hg), and heart rate (beats per minute). All blood pressure measurements during the study should be performed on the same arm, preferably by the same person.

Any clinically significant abnormalities in vital signs noted after Visit 1 will be recorded as AEs in the eCRF.

8.3.7 Electrocardiograms

For screening purposes, a single 12-lead electrocardiogram (ECG) will be obtained using local standard procedures and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA.

8.3.8 Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

- The use of local laboratories is allowed in cases where safety follow-up is considered to be time-sensitive.

8.3.8.1 Renal and Urological Safety Procedures

Urinalysis (including microscopy) will be collected as outlined in the SoA. Participants who have either crystals or unexplained hematuria will be further evaluated. The decision regarding continuing treatment with MK-7264 and/or continued participation in the study will be made on a case-by-case basis in consultation with the Sponsor. Details regarding this process will be provided in a separate document.

8.3.9 Pregnancy Testing

Urine and/or serum pregnancy testing will be performed at the investigator site as indicated in the SoA.

If at any time during the study, the participant's menstrual cycle is 2 weeks later than expected, she will be instructed to perform a UPT at home and contact the clinic to schedule a visit as soon as possible. A clinic visit should be scheduled regardless of the outcome of the UPT. The Sponsor will be consulted as soon as possible. See Section 8.1.9.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE, as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of treatment allocation/randomization through 14 days following cessation of treatment, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered drug-related.

After the post-treatment telephone contact conducted 14 days following cessation of double-blind study intervention, if the investigator becomes aware of any AEs (serious or non-serious) assessed as related to the rescue medication (naproxen sodium), they must be reported to the Sponsor.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. 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.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 3.

Table 3 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period	Reporting Time Period: After the Protocol Specified Follow-up Period	Timeframe to Report Event and Follow-up Information to SPONSOR:
Non-Serious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (Do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AE and/or SAE and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECI), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of 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. All AEs will be reported to regulatory authorities, IRB/IECs, and investigators in accordance with all applicable global laws and regulations (ie, per ICH Topic E6 (R2) Guidelines for Good Clinical Practice [GCP]).

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) 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 (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as

serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

There are no disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs.

8.4.7 Events of Clinical Interest (ECIs)

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

In this study, an overdose of blinded medication is any daily dose higher than 2 tablets. For naproxen sodium, investigator/site personnel are to consult the local approved naproxen sodium label for guidance on the definition of overdose.

No specific information is available on the treatment of overdose of MK-7624. Oral doses of up to 1800 mg bid for 14 days were explored in earlier clinical studies without any untoward clinical effects (see MK-7264 IB). Overdose should be treated according to the participant's clinical signs and symptoms.

Refer to the local label for information regarding treatment of an overdose of naproxen sodium.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

The date and time for the last dose of study treatment taken before the study visit on which the PK sample was collected should be recorded in the eCRF. In addition, the date and time of the PK sample collection should also be recorded in the eCRF.

8.6.1 Blood Collection for Plasma MK-7264

Blood samples will be collected at several visits during the study for determination of MK-7264 as outlined in the SoA.

Visit 4 (randomization): The first sample will be collected pre-dose of study intervention. A second sample will be collected 2 hours after the first dose of study intervention.

Visit 5 and 6: Samples will be collected pre-dose of study intervention at the specified study site visits (ie, the morning dose of study intervention will be taken after the PK sample is collected).

Discontinuation visit: The blood sample may be collected at any time.

Note: If a Discontinuation visit occurs after Visit 6 (PK sample collection), an additional blood sample for PK does not need to be collected.

MK-7264 plasma concentrations will be determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay.

Sample collection, storage, and shipment instructions for plasma samples will be provided in the operations/laboratory manual.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants as specified in the SoA:

- Blood for Genetic Analysis

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the participant signs

the future biomedical research consent. If the planned genetic analysis is not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be provided in the operations/laboratory manual.

8.9 Future Biomedical Research Sample Collection

If the participant signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- Leftover DNA for future research

8.10 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8. Since all study visits will be scheduled around the participant's menses (Visit 1: ~1 to 3 weeks before menses; subsequent visits: ~1 day after end of menses), site staff will need to be in close contact with the participants before Visit 1 and between other clinic visits to monitor the timing of the participant's menses.

8.10.1 Screening

The interval from Visit 1 to Visit 3 will constitute the screening period of approximately 8 weeks. If a participant meets initial entry criteria at Visit 1, she will return to the site for Visit 2 when she will begin using the eDiary and will be provided naproxen sodium rescue medication to use as instructed.

Potential participants will be evaluated at Screening to determine if they fulfill the entry requirements as set forth in Section 5.1 and 5.2 – Inclusion and Exclusion Criteria.

Screening procedures, such as safety labs, may be repeated once at an unscheduled visit if results are inconsistent with the participant's clinical status or recent results. The time period between Visit 1 and V2, may be extended due to the need to repeat screening assessments or timing of menses.

If any participant fails to meet the study entry criteria, screening procedures may be repeated based on investigator judgment after initial screening, and after consultation with the Sponsor. Participants may only be rescreened once. However, participants will not be permitted to rescreen if inclusion criteria for the overall pelvic pain score on the NRS was not met at Visit 1.

8.10.2 Placebo Run-In

Participants will return for Visit 3 on the first non-menstrual day after the SC menses. If the participant meets Visit 3 eligibility criteria, she will enter a single-blind, placebo run-in

period of approximately 4 weeks (ie, the duration of BC). The run-in period will end on the last day of menses of the BC, and the participant will return to the site the next day for Visit 4 (randomization).

8.10.3 Treatment Period

Participants who meet eligibility criteria at Visit 4 will enter the treatment period of approximately 8 weeks, consisting of 2 menstrual cycles (ie, TRC1 and TRC2). The treatment period will start on the first non-menstrual day after the BC menses. The participant will return to the site for Visit 5 the day after the last day of the TRC1 menses. The participant will return to the site for Visit 6 the day after the last day of the TRC2 menses.

8.10.4 Post-Treatment Period

After TRC2, all participants will have 1 additional cycle (~4 weeks) of pain score evaluation only with rescue medication use (if needed). The PTC will start on the first non-menstrual day after the TRC2 menses. During this time, participants will continue to record information in the daily eDiary. Participants will be contacted by telephone approximately 2 weeks after Visit 6 for safety follow up. The participant will return to the site for the final visit (Visit 7), the day after the last day of the last menses.

8.10.5 Discontinued Participants Continuing to be Monitored in the Study

If a participant is discontinued from the study intervention early, the Discontinuation Visit assessments are to be performed as indicated in the SoA.

It is intended that all randomized participants should be followed through completion of the study, regardless of premature discontinuation of treatment, unless the participant withdraws consent from any study follow-up. Thus, participants who discontinue from study intervention before completion of the study should continue to be monitored after the Discontinuation Visit to obtain relevant information through the end of the study.

After the Discontinuation Visit, a telephone contact will be conducted 14 days following cessation of double-blind study intervention during which all reportable safety events as outlined in Section 8.4, Table 3 will be collected. After the 14 day telephone contact, only drug-related SAEs will be collected; in addition, if the investigator becomes aware of any AEs (serious or non-serious) assessed as related to the rescue medication (naproxen sodium), they must be reported to the Sponsor.

Study site visits (or telephone contacts if scheduling of site visits is not possible) should occur at timepoints that correspond to each remaining study visit on the SoA. Only safety events as specified in the paragraph above and concomitant medication information will be collected at these visits. In addition, participants will be asked to continue to provide daily eDiary entries after discontinuation of study intervention; however, if a participant does not agree to continue using the eDiary, she will still be followed for collection of safety events as specified above and concomitant medication information.

Concomitant therapies specifically prohibited (see Table 1) while the participant was on study intervention are no longer prohibited after discontinuation of study intervention.

For these participants who have discontinued study intervention early, sites will be instructed to exert diligent efforts to continue to contact them. To enable sites to reach participants, the participants should provide primary and secondary contact information (eg, home phone, work phone, mobile phone). Sites must document the outcome of the telephone contact(s), to demonstrate diligent efforts have been made. If a participant does not agree to be contacted for follow-up for each of the remaining visits (as described in Section 7.1 – Discontinuation of Study Intervention), the participant should be encouraged to accept a telephone contact at least at the final visit date (ie, Visit 7).

Additionally, the ICF will explain the importance of continued data collection from participants, including the use of continued contact by phone.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding/final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in a supplemental statistical analysis plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Separate analysis plans (ie, separate documents from the sSAP) will be developed to detail other planned analyses including those specific to the analysis of PK data and participant-reported outcomes.

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized below. The comprehensive plan is provided in Sections 9.2-9.12.

Study Design Overview	A Phase 2a, Proof of Concept, Randomized, Double-blind, Placebo-controlled Clinical Trial, to Evaluate the Efficacy and Safety of MK-7264 in Women with Moderate to Severe Endometriosis-related Pain
Treatment Assignment	Participants will be randomized in a 1:1 ratio to MK-7264 or placebo. Randomization will be stratified according to the following factors: moderate pelvic pain (score of ≥5 to <8 on the NRS in the eDiary at baseline cycle) or severe pelvic pain (score of ≥8 on the NRS in the eDiary at baseline cycle).
Analysis Populations	Efficacy: Full Analysis Set (FAS) population. Safety: All Participants as Treated (APaT) population.
Primary Endpoint	Efficacy: Average daily pelvic pain scores (cyclic and non-cyclic) during TRC2. Safety: • The proportion of participants with adverse events (AEs) • The proportion of participants with an AE which leads to discontinuation
Statistical Methods for Key Efficacy Analyses	The primary analysis approach will be conducted utilizing the longitudinal analysis of covariance (ANCOVA) model. In this model, the response vector consists of the change from baseline in the average daily pelvic pain score during TRC1 and TRC2. The model will include factors for average pelvic pain scores at baseline cycle, stratum, treatment, cycle, interaction of stratum-by-cycle, and the interaction of treatment-by-cycle as covariates. The model will use all available daily scores for calculating average pain scores during TRC1 and TRC2. The least squares (LS) mean change from baseline with the associated standard errors (SEs) will be displayed for each treatment group. Estimated treatment differences (MK-7264 − placebo) along with corresponding 95% CIs will also be presented.
Statistical Methods for Key Safety Analyses	The analysis of safety endpoints will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. Tier 1 safety endpoints will be subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-group comparisons. Tier 2 safety endpoints will be evaluated via point estimates and 95% CIs for between-group comparisons. Tier 3 safety endpoints will be evaluated via point estimates only.

Interim Analyses (IA)	This study is designed as a group sequential trial with one interim analysis and a final analysis. The interim analysis will be planned for the primary endpoint when 84 participants have been enrolled and completed TRC2 (ie, 60% of the participants who are expected to complete TRC2). A non-binding futility criterion will be used based on the futility boundary using an O'Brien-Fleming like beta error spending function (Hwang, Shih, deCani gamma = -4), and the results will be reviewed by a SiDMC. At the IA, if the one-sided p-value is ≥ 0.340, which is equivalent to observe that the treatment difference (MK-7264 - placebo) in change from baseline in average daily pelvic pain scores during TRC2 is greater than -0.180 point (given the assumed Standard Deviation [SD]), the study enrollment may be terminated in support of an overall conclusion of futility. No interim analyses for safety will be planned for this protocol.
Multiplicity	No adjustment will be made for multiplicity.
Sample Size and Power	166 participants (83 in each group) will be randomized in this study, and the expected drop-out rate is 15%. Then 140 evaluable participants (70 participants in each group) will provide 84% power to detect a difference of 1 point between MK-7264 and placebo during TRC2, in change from baseline of the average daily pelvic pain score in the NRS, with one IA conducted when 84 participants have been enrolled and completed TRC2 or 60% of the participants who are expected to complete TRC2. This power calculation is based on a two-sided test with Type I error 0.05. The sensitivity assessment of the power on the assumptions of dropout rate and SD are provided in Section 9.9.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the designee of the Sponsor.

The study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment.

Blinding issues related to the planned interim analyses are described in Section 9.7.

9.3 Hypotheses/Estimation

The primary hypothesis for this study is stated in Section 3.

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

Primary Efficacy Endpoint

- Average daily pelvic pain scores (cyclic and non-cyclic) during TRC2

Secondary Efficacy Endpoints

- Average daily cyclic pelvic pain scores during TRC2
- Average daily non-cyclic pelvic pain scores during TRC2

Exploratory Efficacy Endpoints

- Average daily use of naproxen sodium rescue medication by number of tablets taken for daily pelvic pain (cyclic and non-cyclic, combined and separately) during TRC2
- Proportion of participants with at least 1-point (2, or 3) reduction in average daily pelvic pain score (cyclic and non-cyclic, combined and separately) as compared to baseline
- Proportion of participants with at least 1-point (2, or 3) reduction in average daily pelvic pain score (cyclic and non-cyclic, combined and separately) as compared to baseline, and no increase in the average daily use of rescue medication by number of tablets
- Proportion of participants with at least 1-point (2, or 3) reduction in average daily pelvic pain score (cyclic and non-cyclic, combined and separately) as compared to baseline, no increase in the average daily use of rescue medication by number of tablets, and no use of concomitant pain medication
- Proportion of participants with at least 1-point (2, or 3) reduction in average daily pelvic pain score (cyclic and non-cyclic, combined and separately) as compared to baseline, no increase in the average daily use of rescue medication by number of tablets, and no use of concomitant pain medication for ERP
- Average daily pelvic pain scores (cyclic and non-cyclic) during PTC
- Average daily pelvic pain scores (cyclic and non-cyclic) during TRC1

- Number of days with no impact (score=0) of endometriosis-related pain at TRC2 on each of the following items, separately: work/school, physical activities, leisure/social activities, and sleep.

- Patient's Global Impression of Change ratings at TRC2

- Endometriosis Health Profile-5 at TRC2

9.4.2 Safety Endpoints

A description of safety measures is contained in Sections 8.3 and 8.4. The analysis of safety results is described in Section 9.6.2.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory values, vital signs, and body weight.

The a priori safety endpoint(s) of interest are: Taste related AEs (including dysgeusia, ageusia, and hypogeusia).

9.4.3 **Pharmacokinetic** Endpoints

Plasma pharmacokinetic parameters, Cmax and AUC, will be estimated using the population model developed using Phase 1 and Phase 2 data.

An exploratory analysis may be conducted to understand the pharmacokinetic and efficacy relationship.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized participants who have received at least one dose of double-blind study treatment and had at least one day of eDiary entry during the treatment cycle post randomization.

The modified Full Analysis Set (mFAS) population will be used as a supportive population for primary and secondary efficacy endpoints. The mFAS population consists of all randomized participants who have received at least one dose of double-blind study treatment, and had at least 10 days of eDiary entries in each of the treatment cycles post randomization.

The completer population will be used as a supportive population for primary and secondary efficacy endpoints, and will be used for the planned interim analysis. The completer population consists of all randomized participants who have completed the TRC2.

The Per-Protocol (PP) population will be used as another supportive population for primary and secondary efficacy endpoints. The PP population excludes participants from FAS due to important deviations from the protocol that may substantially affect the results of the

primary/secondary efficacy endpoint(s). Potential deviations that may result in the exclusion of a participant from the Per-Protocol population include:

- Compliance with <75% of eDiary daily entries
- No daily pelvic pain scores during TRC2

The final determination on protocol deviations will be made prior to the final unblinding of the database.

9.5.2 Safety Analysis Populations

Safety Analyses will be conducted in the All Participants as Treated (APaT) population, which consists of all randomized participants who received at least one dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study treatment for the entire treatment period; such participants will be included in the treatment group corresponding to the study treatment actually received.

The evaluable PK population for PK data analysis is defined as all participants with one measurable PK sample.

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the supplemental SAP.

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. The primary analysis will be based on the FAS population, and supportive analyses will be based on the mFAS, Completer population and PP population.

The primary efficacy endpoint is the average daily pelvic pain score during TRC2. The variable of change from baseline in the average daily pelvic pain score will be used in the analysis of the primary endpoint. The primary analysis approach will be conducted utilizing the longitudinal analysis of covariance (ANCOVA) model. In this model, the response vector consists of the change from baseline in the average daily pelvic pain scores during TRC1 and TRC2. The model will include factors for average pelvic pain scores at baseline cycle, stratum, treatment, cycle, interaction of stratum-by-cycle, and the interaction of treatment-by-cycle as covariates. The model will use all available daily scores for calculating average pain scores during TRC1 and TRC2. The least-squares (LS) mean change from baseline at TRC2 with the associated standard errors (SEs) will be displayed for each treatment group; and the estimated treatment differences (MK-7264 − placebo) along with corresponding 95% CIs will also be presented.

The average daily pelvic pain score during TRC1 will be analyzed from the same model, and the LS mean (SEs, and 95% CIs) will be presented in the same way.

The secondary endpoints will be analyzed in the same way as the primary endpoint.

Table 4 summarizes the key analyses strategies of the primary and secondary efficacy endpoints.

Table 4 Statistical Methods for Efficacy Endpoints

Endpoint/Variable (During TRC2)	Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary				
Average daily pelvic pain scores during TRC2	P	Longitudinal ANCOVA	FAS	Observed data only
	S	Longitudinal ANCOVA	mFAS/Completer Population/PP	Observed data only
	S	Longitudinal ANCOVA	FAS	Jump to reference imputation
Secondary				
Average daily cyclic pelvic pain scores during TRC2	P	Longitudinal ANCOVA	FAS	Observed data only
	S	Longitudinal ANCOVA	mFAS/Completer Population/PP	Observed data only
	S	Longitudinal ANCOVA	FAS	Jump to reference imputation
Average daily non-cyclic pelvic pain scores during TRC2	P	Longitudinal ANCOVA	FAS	Observed data only
	S	Longitudinal ANCOVA	mFAS/Completer Population/PP	Observed data only
	S	Longitudinal ANCOVA	FAS	Jump to reference imputation

ANCOVA = Analysis of covariance; FAS = Full Analysis Set; mFAS=modified Full Analysis Set; PP = Per Protocol
P = Primary; S = Supportive.

For the continuous endpoints for the exploratory objectives, similar statistical approaches will be used as described above for the primary endpoint. For the proportions in the exploratory endpoints, they will be analyzed by logistic-regression models comparing MK-7264 with placebo, including average pelvic pain scores at baseline cycle, stratum, treatment, cycle, interaction of stratum-by-cycle, and the interaction of treatment-by- cycle as covariates.

Additionally, change from baseline in average daily pelvic pain score (cyclic and non-cyclic, combined and separately) on days with rescue medication versus days without use rescue medication will also be summarized.

Handling of Missing Data

Sensitivity analyses will be conducted to incorporate methods for handling missing data due to participant who discontinue the trial. The missing data will be imputed based on jump-to-reference method, that is, the missing scores in each treatment group will be imputed from the placebo group. The multiple-imputation (MI) approach will be used and the details will be documented in sSAP.

9.6.2 Statistical Methods for Safety Analyses

The APaT population will be used for all safety analyses. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory values, vital signs, and body weight.

The analysis of safety results will follow a tiered approach (Table 5). The tiers differ with respect to the analyses that will be performed. Tier 1 safety endpoints will be subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-group comparisons. Tier 2 safety endpoints will be evaluated via point estimates and 95% CIs for between-group comparisons. Tier 3 safety endpoints will be evaluated via point estimates only.

Tier 1 Events

Safety parameters or adverse events of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals to be provided for between-treatment differences in the proportion of participants with events; these analyses will be performed using the Miettinen and Nurminen (M&N) method (1985), an unconditional, asymptotic method. For this protocol, Taste-related AEs (including dysgeusia, ageusia, and hypogeusia, as well as other related terms) are considered Tier 1 events.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for differences in the proportion of participants with events (also via the M&N method (1985).

Membership in Tier 2 requires that at least 4 participants in any treatment group exhibit the event. The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals for Tier 2 events may be provided without adjustment for multiplicity, the confidence

intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse events and safety parameters that meet predefined limits of change.

In addition to individual events that occur in 4 or more participants in any treatment group, the broad AE categories consisting of the proportion of participants with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, and discontinuation due to an AE will be considered Tier 2 endpoints.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Table 5 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Taste related AE (including dysgeusia, ageusia, and hypogeusia)	X	X	X
Tier 2	Any AE		X	X
	Any Serious AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Any discontinuation due to AE		X	X
	Any discontinuation due to Serious AE		X	X
	Any discontinuation due to Drug-Related AE		X	X
	Any discontinuation due to Serious Drug-Related AE		X	X
	Specific AEs (incidence ≥ 4 participants in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs, or PDLCs [1] (incidence < 4 participants in both treatment groups)			X
	Change from Baseline Results (Lab data, Vital Signs and Body Weight)			X

[1] Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier-2 endpoints.
Note: AE = Adverse Event; SOC=System Organ Class; PDLC=predefined limit of change; X = results will be provided.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory, vital signs, and body weights, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the summary statistics. No statistical hypothesis tests will be performed on these characteristics.

Demographics and baseline characteristics include age, race, ethnicity, body weight, height, BMI (weight/height^2 in kg/m^2), medical history, gynecological history, and prior and concomitant medications. All variables will be summarized by treatment group either by descriptive statistics or categorical tables.

The number and percentage of participants screened and randomized, the primary reasons for screening failure, and the primary reasons for discontinuation will be tabulated. The number of participants who were treated and completed the clinical trial will also be tabulated.

9.7 Interim Analyses

Treatment-level results and/or participant-level data from the interim analysis will be provided by the unblinded statistician to the standing internal Data Monitoring Committee (siDMC) which consists of SPONSOR personnel. Limited additional SPONSOR personnel may be unblinded to the treatment level results of the interim analysis, if required, in order to act on the recommendations of the siDMC. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician.

The processes by which recommendations and decisions are reached and communicated are documented in the siDMC charter for the SPONSOR**.** The protocol-specific siDMC charter will be referenced in the CSR. Prior to final study unblinding, individuals who have been unblinded at any level will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

This study is planned to have one interim analysis for futility and a final analysis. The interim analysis will be planned for the primary endpoint when 84 participants have been enrolled and completed TRC2 (60% of the participants who are expected to complete TRC2). The Completer Population (see Section 9.5.1) will be used for the assessment of evidence for futility. A non-binding futility criterion will be used based on the futility boundary using O'Brien-Fleming like beta error spending function (Hwang, Shih, deCani gamma = -4). This is a conservative approach which will spend 2.8% beta error (Type II error) at the IA and the results will be reviewed by the SiDMC. During the futility analysis the enrollment of participants will continue.

At the IA, if the one-sided p-value is $\geq$ 0.340, which is equivalent to observing that the treatment difference (MK-7264 - placebo) in change from baseline in average daily pelvic pain scores during TRC2 is greater than -0.180 point (Table 6), the study enrollment may be

terminated in support of an overall conclusion of futility. The criterion and the boundary properties for the IA are given in Table 6.

Table 6 Boundary Properties for Planned Interim Analysis

Analysis	Value	Futility
IA: 84‡ participants or 60% of the participants who are expected to complete TRC2	Z	-0.413
	Nominal p-value	0.340
	delta at bound§§	-0.180
	P(Cross) if delta=0§	0.660
	P(Cross) if delta=-1#	0.030

‡ The number of 84 participants is 60% of the 140 participants who are expected to complete TRC2, which can provide power 84% for this study.
§§ The difference in change from baseline between MK-7264 and placebo.
§ The probability of crossing the futility bound when the true difference is 0 (null hypothesis).
# The probability of crossing the futility bound when the true difference is -1 (assumed true difference for power calculation).

No Interim analyses for safety will be planned for this protocol.

9.8 Multiplicity

No adjustment will be made for multiplicity.

9.9 Sample Size and Power Calculations

166 participants (83 in each group) will be randomized in this study, and the expected drop-out rate is 15%. Then 140 evaluable participants (70 participants in each group) will provide 84% power to detect a difference of 1 point between MK-7264 and placebo during TRC2, in change from baseline of the average daily pelvic pain score in the NRS, with one IA conducted when 84 participants have been enrolled and completed TRC2 or 60% of the participants who are expected to complete TRC2. This power calculation is based on a two-sided test with Type I error 0.05. The drop-out rate is from previous trials in chronic cough of MK-7264, and there is limited data to estimate the drop-out rate for ERP. Table 7 provides the power calculations for different assumptions of drop-out rate with the randomized participants.

Table 7 Power Calculation Based on Different Dropout Rates

Number of Randomized Participants	Dropout Rate	Number of Evaluable Participants	Power
166	10%	149	86%
	12%	146	85%
	15% (expected)	140	84%
	20%	132	82%

The assumption of the 1 point difference between MK-7264 and placebo, and the common standard deviation (SD) of 2 units are based on a publication by Diamond [Diamond, M. P., et al 2013]. Table 8 provides the power calculations for different assumptions of SD with the sample size.

Table 8 Power Calculation for Different Assumptions of SD with 140 Evaluable Subjects

Difference	SD	power
1	2.5	66%
1	2	84%
1	1.5	98%
1	1	100%

9.10 Subgroup Analyses

Analysis for the primary and secondary efficacy endpoints will be provided for the following subgroups of baseline factors:

- Age category (18 – 30, 31 – 49 years).
- Pain intensity: NRS in the eDiary moderate (score: ≥ 5 to <8) and severe (score: ≥8) at baseline.
- Geographic region (US versus ex-US)

Additional subgroup analysis will be provided for change from baseline in average daily use of rescue medication by geographic region (US versus ex-US).

9.11 Compliance (Medication Adherence)

For each participant, percent compliance will be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should Be on Therapy}} \times 100\%$$

A day within the study will be considered an "On-Therapy" day if the participant takes all required medication. When a participant takes less than or more than the required medication on a day, that day is not considered an "On-Therapy" day.

For participants who are followed for the entire study period, the "Number of Days Should be on Therapy" is the number of days from the first scheduled treatment day to the last scheduled treatment day. For participants who discontinue from the study, the "Number of Days Should be on Therapy" is the number of days from the first scheduled treatment day to the last dose day.

Summary statistics will be provided on percent compliance for the APaT population.

9.12 Extent of Exposure

The duration of treatment for each participant will be evaluated by calculating the number of days on therapy. Exposure to study intervention will be summarized using descriptive statistics (ie, mean, SD, median, minimum, and maximum) for the APaT population.

Confidential

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10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing, in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Ethics Committee Review (Institutiona Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may

wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

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

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.

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.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or

committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF report form data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Internal Data Monitoring Committee

To supplement the routine monitoring outlined in this protocol, a separate Standing Internal Data Monitoring Committee (siDMC) will monitor the interim data from this study. The siDMC is comprised of members of Sponsor Senior Management, none of whom are directly associated with the conduct of this study. The siDMC will monitor the study at an appropriate frequency (Section 9.7 [Interim Analyses]) for evidence of futility, as described in the detailed monitoring guidelines. The siDMC will determine whether the study should continue according to the protocol.

Specific details regarding responsibilities of the siDMC will be described in a separate charter that is reviewed and approved by the siDMC.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. 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.

If publication activity is not directed by the Sponsor, 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.

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarmen

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study. The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Studies.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.8 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 (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

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

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and 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.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 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.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study 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 entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 9 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine eGFR will be calculated with each serum creatinine measurement (using the CKD EPI formula [http://mdrd.com/]	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] Microscopic examination (all crystals will be characterized)			
Other Screening Tests	Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP)			

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

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

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, 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) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent, or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, 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.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

- The term "life-threatening" in the definition of "serious" refers to an event in which the 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**

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

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

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 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 in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- 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 blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- 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.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) 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 (for pediatric studies, awareness of symptoms, but easily tolerated).
  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).
  - 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 used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product cause the AE?
- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:
  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

- If yes, did the AE resolve or improve?
- If yes, this is a positive dechallenge.
- If no, this is a negative dechallenge.

(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?
  - If yes, did the AE recur or worsen?
  - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship:
    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship:
    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- 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 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by 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.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference Section 8.4.1 for reporting time requirements.
- 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 EDC 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 EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, 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 not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Not applicable

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10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

- A woman is considered fertile after menarche and until becoming postmenopausal unless permanently sterile. All participants in this study are WOCBP and must follow the contraception requirements below.
    - This includes women with tubal infertility from endometriosis.
- **Exception**: Women who have had a documented bilateral salpingectomy may participate in the study, but do not have to follow protocol-specified contraception requirements.

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

10.5.2 Contraception Requirements

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

- Is heterosexually abstinent;

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

  OR

- Is heterosexually active and agrees to use two of the following barrier contraception methods consistently and correctly during the protocol-defined time frame in Section 5.1: male condom, female condom, cervical cap, diaphragm, sponge, or spermicide.

  Note: Hormonal contraception except for sporadic use of emergency contraception is not permitted during the study. Male and female condoms should not be used at the same time.

  OR

- Has undergone bilateral tubal sterilization;

  OR

- Has a vasectomized partner.

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

10.5.3 Pregnancy Testing

Study participants should only be included after a negative highly sensitive urine and serum pregnancy test at Visit 1 and at Visit 4 (randomization). In between these visits, urine pregnancy testing will be performed at Visit 2 and 3. After randomization, additional pregnancy testing will be performed as indicated on the SoA (Section 1.3). At visits in which only a urine pregnancy test is indicated on the SoA, a serum pregnancy test will also be required when a pregnancy is suspected or when a urine pregnancy test is positive, unless pregnancy has already been confirmed by ultrasound.

If any menstrual cycle is 2 weeks later than expected, the participant must perform a urine pregnancy test at home and contact the clinic to schedule a visit as soon as possible. The Sponsor must be consulted.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research.

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in the future biomedical research substudy

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit

designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this substudy. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized and are described in the Future Biomedical Research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@merck.com.

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10.7 Appendix 7: Country-specific Requirements

Not applicable

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10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
AE	Adverse event
ANCOVA	Analysis of covariance
APaT	All participants as treated
ATP	Adenosine triphosphate
AUC50	Area under the curve required to achieve 50% of the maximal response
bid	Twice daily
BC	Baseline Cycle
BMI	Body mass index
BPS	Bladder pain syndrome
CHC	Combined hormonal contraceptive
CRF	Case Report Form
CSR	Clinical Study Report
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECI	Events of clinical interest
eCRF	Electronic Case Report Form
EDC	Electronic data collection
eDiary	Electronic diary
EHP-5	Endometriosis Health Profile-5
EMA	European Medicines Agency
ePRO	Electronic patient reported outcome
ERP	Endometriosis-related pain
FAS	Full analysis set
GCP	Good Clinical Practice
GnRH	Gonadotropin-releasing hormone
hCG	Human chorionic gonadotropin
IB	Investigator's Brochure
IA	Interim analysis
IC	Interstitial cystitis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive response technology
IUD	Intrauterine device
LS	Least squares
MI	Multiple imputation
NRS	Numeric rating scale
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic
PoC	Proof of concept
PP	Per-protocol
PPI	Proton pump inhibitor
PTC	Post-treatment Cycle
SAE	Serious adverse event

Abbreviation	Expanded Term
SAP	Statistical analysis plan
SC	Screening Cycle
SD	Standard deviation
SE	Standard error
SiDMC	Standing Internal Data Monitoring Committee
SoA	Schedule of activities
sSAP	Supplemental statistical analysis plan
TRC1	Treatment Cycle 1
TRC2	Treatment Cycle 2
UPT	Urine pregnancy test
WOCBP	Woman/women of childbearing potential

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Supplemental Statistical Analysis Plan (sSAP)

Protocol Title: A Phase 2a, Proof of Concept, Randomized, Double-blind, Placebo-controlled Clinical Trial, to Evaluate the Efficacy and Safety of MK-7264 in Women with Moderate to Severe Endometriosis-related Pain

TABLE OF CONTENTS

LIST OF TABLES

1. INTRODUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of confirmatory analyses for this trial, this supplemental SAP provides additional statistical analysis details/data derivations and documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

2. SUMMARY OF CHANGES

This document is the first version of the sSAP.

3. ANALYTICAL AND METHODOLOGICAL DETAILS

3.1 STATISTICAL ANALYSIS PLAN SUMMARY

Key elements of the SAP are summarized below. The comprehensive plan is provided in Sections 3.2-3.12.

Study Design Overview	A Phase 2a, Proof of Concept, Randomized, Double-blind, Placebo-controlled Clinical Trial, to Evaluate the Efficacy and Safety of MK-7264 in Women with Moderate to Severe Endometriosis-related Pain
Treatment Assignment	Participants will be randomized in a 1:1 ratio to MK-7264 or placebo. Randomization will be stratified according to the following factors: moderate pelvic pain (score of ≥5 to <8 on the NRS in the eDiary at baseline cycle) or severe pelvic pain (score of ≥8 on the NRS in the eDiary at baseline cycle).
Analysis Populations	Efficacy: Full Analysis Set (FAS) population. Safety: All Participants as Treated (APaT) population.
Primary Endpoint	Efficacy: Average daily pelvic pain scores (cyclic and non-cyclic) during TRC2. Safety: • The proportion of participants with adverse events (AEs) • The proportion of participants with an AE which leads to discontinuation
Statistical Methods for Key Efficacy Analyses	The primary analysis approach will be conducted utilizing the longitudinal analysis of covariance (ANCOVA) model. In this model, the response vector consists of the change from baseline in the average daily pelvic pain score during Treatment Cycle 1 (TRC1) and Treatment Cycle 2 (TRC2). The model will include factors for average pelvic pain scores at baseline cycle, stratum, treatment, cycle, interaction of stratum-by-cycle, and the interaction of treatment-by-cycle as covariates. The model will use all available daily scores for calculating average pain scores during TRC1 and TRC2. The least squares (LS) mean change

	from baseline with the associated standard errors (SEs) will be displayed for each treatment group. Estimated treatment differences (MK-7264 − placebo) along with corresponding 95% CIs will also be presented.
Statistical Methods for Key Safety Analyses	The analysis of safety endpoints will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. Tier 1 safety endpoints will be subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-group comparisons. Tier 2 safety endpoints will be evaluated via point estimates and 95% CIs for between-group comparisons. Tier 3 safety endpoints will be evaluated via point estimates only.
Interim Analyses (IA)	This study is designed as a group sequential trial with one interim analysis and a final analysis. The interim analysis will be planned for the primary endpoint when 84 participants have been enrolled and completed TRC2 (ie, 60% of the participants who are expected to complete TRC2). A non-binding futility criterion will be used based on the futility boundary using an O'Brien-Fleming like beta error spending function (Hwang, Shih, deCani gamma = -4), and the results will be reviewed by a SiDMC. At the IA, if the one-sided p-value is ≥ 0.340, which is equivalent to observe that the treatment difference (MK-7264 - placebo) in change from baseline in average daily pelvic pain scores during TRC2 is greater than -0.180 point (given the assumed Standard Deviation [SD]), the study enrollment may be terminated in support of an overall conclusion of futility. No interim analyses for safety will be planned for this protocol.
Multiplicity	No adjustment will be made for multiplicity.
Sample Size and Power	166 participants (83 in each group) will be randomized in this study, and the expected drop-out rate is 15%. Then 140 evaluable participants (70 participants in each group) will provide 84% power to detect a difference of 1 point between MK-7264 and placebo during TRC2, in change from baseline of the average daily pelvic pain score in the NRS, with one IA conducted when 84 participants have been enrolled and completed TRC2 or 60% of the participants who are expected to complete TRC2. This power calculation is based on a two-sided test with Type I error 0.05. The sensitivity assessment of the power on the assumptions of dropout rate and SD are provided in Section 3.9.

3.2 RESPONSIBILITY FOR ANALYSES/IN-HOUSE BLINDING

The statistical analysis of the data obtained from this study will be the responsibility of the designee of the Sponsor.

The study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment.

Blinding issues related to the planned interim analyses are described in Section 3.7.

3.3 HYPOTHESES/ESTIMATION

The primary hypothesis for this study is stated in Section 3 of Protocol.

3.4 ANALYSIS ENDPOINTS

3.4.1 Efficacy Endpoints

Primary Efficacy Endpoint

- Average daily pelvic pain scores (cyclic and non-cyclic) during TRC2

Secondary Efficacy Endpoints

- Average daily cyclic pelvic pain scores during TRC2
- Average daily non-cyclic pelvic pain scores during TRC2

Exploratory Efficacy Endpoints

- Average daily use of naproxen sodium rescue medication by number of tablets taken for daily pelvic pain (cyclic and non-cyclic, combined and separately) during TRC2
- Proportion of participants with at least 1-point (2, or 3) reduction in average daily pelvic pain score (cyclic and non-cyclic, combined and separately) as compared to baseline during TRC2
- Proportion of participants with at least 1-point (2, or 3) reduction in average daily pelvic pain score (cyclic and non-cyclic, combined and separately) as compared to baseline during TRC2, and no increase in the average daily use of rescue medication by number of tablets
- Proportion of participants with at least 1-point (2, or 3) reduction in average daily pelvic pain score (cyclic and non-cyclic, combined and separately) as compared to baseline

during TRC2, no increase in the average daily use of rescue medication by number of tablets, and no use of concomitant pain medication

- Proportion of participants with at least 1-point (2, or 3) reduction in average daily pelvic pain score (cyclic and non-cyclic, combined and separately) as compared to baseline during TRC2, no increase in the average daily use of rescue medication by number of tablets, and no use of concomitant pain medication for ERP
- Average daily pelvic pain scores (cyclic and non-cyclic, combined and separately) during PTC
- Average daily pelvic pain scores (cyclic and non-cyclic, combined and separately) during TRC1
- Number of days with no impact (score=0) of endometriosis-related pain at TRC2 on each of the following items, separately: work/school, physical activities, leisure/social activities, and sleep.
- Patient's Global Impression of Change ratings at TRC2
- Endometriosis Health Profile-5 at TRC2

3.4.2 Safety Endpoints

A description of safety measures is contained in Sections 8.3 and 8.4. The analysis of safety results is described in Section 3.6.2.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory values, vital signs, and body weight.

The a priori safety endpoint(s) of interest are: Taste related AEs (including dysgeusia, ageusia, and hypogeusia).

3.4.3 Pharmacokinetic Endpoints

Plasma pharmacokinetic parameters, Cmax and AUC, will be estimated using the population model developed using Phase 1 and Phase 2 data.

An exploratory analysis may be conducted to understand the pharmacokinetic and efficacy relationship.

3.5 ANALYSIS POPULATIONS

3.5.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized participants who have received at least one dose of double-blind study treatment and had at least one day of eDiary entry during the treatment cycle post randomization.

The modified Full Analysis Set (mFAS) population will be used as a supportive population for primary and secondary efficacy endpoints. The mFAS population consists of all randomized participants who have received at least one dose of double-blind study treatment, and had at least 10 days of eDiary entries in each of the treatment cycles post randomization.

The completer population will be used as a supportive population for primary and secondary efficacy endpoints, and will be used for the planned interim analysis. The completer population consists of all randomized participants who have completed the TRC2.

The Per-Protocol (PP) population will be used as another supportive population for primary and secondary efficacy endpoints. The PP population excludes participants from FAS due to important deviations from the protocol that may substantially affect the results of the primary/secondary efficacy endpoint(s). Potential deviations that may result in the exclusion of a participant from the Per-Protocol population include:

- Compliance with <75% of eDiary daily entries
- No daily pelvic pain scores during TRC2

For each participant, percent eDiary compliance will be calculated using the following formula:

$$\text{eDiary Compliance (\%)} = \frac{\text{Number of days with eDiary daily entries}}{\text{Number of expected days with eDiary daily entries}} \times 100$$

The number of days with eDiary daily entries (numerator) is the number of days with eDiary daily entries during overall trial period (i.e., from the date of Visit 2 to one day before the date of Visit 7/Discontinuation) and the number of expected days with eDiary daily entries (denominator) is the number of days during overall trial period (i.e., from the date of Visit 2 to one day before the date of Visit 7/Discontinuation).

The final determination on protocol deviations will be made prior to the final unblinding of the database.

3.5.2 Safety Analysis Populations

Safety Analyses will be conducted in the All Participants as Treated (APaT) population, which consists of all randomized participants who received at least one dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study treatment for the entire treatment period; such participants will be included in the treatment group corresponding to the study treatment actually received.

At least one laboratory, vital sign, weight, or height measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

The evaluable PK population for PK data analysis is defined as all participants with one measurable PK sample.

3.6 STATISTICAL METHODS

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in Section 3.6.1.

3.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. The primary analysis will be based on the FAS population, and supportive analyses will be based on the mFAS, Completer population and PP population.

The efficacy analyses will be performed based on the available data during 5 cycles, defined as below:

- Screening Cycle (SC):
  - Starts the first non-bleeding day of the SC (i.e., 1 day after the last day of the menses before Visit 2) and ends the last bleeding day of SC.
- Baseline Cycle (BC) placebo run-in period:
  - Starts on the first non-bleeding day of the BC (i.e., 1 day after the last bleeding day of the SC) and ends the last bleeding day of BC.
- TRC1 after randomization:
  - Starts on Day 1(i.e., the first study medication intervention) and ends the last bleeding day of TRC1.
- TRC2:
  - Starts on the first non-bleeding day of TRC2 (i.e.,1 day after the last bleeding day of the TRC1) and ends the last bleeding day of TRC2.
- Post-Treatment Cycle (PTC) after the participant has stopped taking study intervention:
  - Starts on the first non-bleeding day of PTC (i.e.1 day after the last bleeding day of the TRC 2) or the day after the last dose of study medication, whichever is last and ends the last bleeding day of PTC.

Primary Efficacy Analysis

The primary efficacy endpoint is the average daily pelvic pain score during TRC2. The variable of change from baseline in the average daily pelvic pain score will be used in the analysis of the primary endpoint. The primary analysis approach will be conducted utilizing the longitudinal analysis of covariance (ANCOVA) model. In this model, the response vector consists of the change from baseline in the average daily pelvic pain scores during TRC1 and

TRC2. The model will include factors for average pelvic pain scores at baseline cycle, stratum, treatment, cycle, interaction of stratum-by-cycle, and the interaction of treatment-by-cycle as covariates. The model will use all available daily scores for calculating average pain scores during TRC1 and TRC2. The least-squares (LS) mean change from baseline at TRC2 with the associated standard errors (SEs) will be displayed for each treatment group; and the estimated treatment differences (MK-7264 − placebo) along with corresponding 95% CIs will also be presented.

Secondary Efficacy Analyses

The secondary endpoints will be analyzed in the same way as the primary endpoint.

Table 1 summarizes the key analyses strategies of the primary and secondary efficacy endpoints.

Table 1 Statistical Methods for Efficacy Endpoints

Endpoint/Variable (During TRC2)	Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary				
Average daily pelvic pain scores during TRC2	P	Longitudinal ANCOVA	FAS	Observed data only
	S	Longitudinal ANCOVA	mFAS/Completer Population/PP	Observed data only
	S	Longitudinal ANCOVA	FAS	Jump to reference imputation
Secondary				
Average daily cyclic pelvic pain scores during TRC2	P	Longitudinal ANCOVA	FAS	Observed data only
	S	Longitudinal ANCOVA	mFAS/Completer Population/PP	Observed data only
	S	Longitudinal ANCOVA	FAS	Jump to reference imputation
Average daily non-cyclic pelvic pain scores during TRC2	P	Longitudinal ANCOVA	FAS	Observed data only
	S	Longitudinal ANCOVA	mFAS/Completer Population/PP	Observed data only
	S	Longitudinal ANCOVA	FAS	Jump to reference imputation
ANCOVA = Analysis of covariance; FAS = Full Analysis Set; mFAS=modified Full Analysis Set; PP = Per Protocol P = Primary; S = Supportive.				

Exploratory Efficacy Analyses

- For the continuous endpoints for the exploratory objectives, similar statistical approaches will be used as described above for the primary endpoint. Average daily use of naproxen sodium rescue medication in terms of number of tablets taken for daily pelvic pain (cyclic and non-cyclic, combined and separately) as compared to baseline during TRC2:

  From the longitudinal ANCOVA model, the response vector consists of the change from baseline in the average daily use of naproxen sodium rescue medication during TRC1and TRC2. The model will include factors for average daily use of naproxen sodium rescue medication at baseline cycle, stratum, treatment, cycle, interaction of stratum-by-cycle, and the interaction of treatment-by- cycle as covariates.

- Average daily pelvic pain scores (cyclic and non-cyclic, combined and separately) as compared to the Screening Cycle during PTC:

  From the longitudinal ANCOVA model, the response vector consists of the change from screening cycle in the average daily pelvic pain scores during BC, TRC1, TRC2, and PTC. The model will include factors for average pelvic pain scores at screening cycle, stratum, treatment, cycle, interaction of stratum-by-cycle, and the interaction of treatment-by- cycle as covariates. The LS mean (SEs, and 95% CIs) will be presented.

- Average daily pelvic pain scores (cyclic and non-cyclic, combined and separately) as compared to baseline during TRC1:

  The average daily pelvic pain score during TRC1 will be analyzed from the same model (including response vector and covariates) for the primary endpoint, and the LS mean (SEs, and 95% CIs) will be presented in the same way.

For the proportions in the following exploratory endpoints, they will be analyzed by logistic-regression models comparing MK-7264 with placebo, including average pelvic pain scores at baseline cycle, stratum, treatment, cycle, interaction of stratum-by-cycle, and the interaction of treatment-by- cycle as covariates.

- Proportion of participants with at least 1-point (2, or 3) reduction in average daily pelvic pain score (cyclic and non-cyclic, combined and separately) as compared to baseline during TRC2.

- Proportion of participants with at least 1-point (2, or 3) reduction in average daily pelvic pain score (cyclic and non-cyclic, combined and separately) as compared to baseline during TRC2, and no increase in the average daily use of rescue medication by number of tablets.

- Proportion of participants with at least 1-point (2, or 3) reduction in average daily pelvic pain score (cyclic and non-cyclic, combined and separately) as compared to baseline

during TRC2, no increase in the average daily use of rescue medication by number of tablets, and no use of concomitant pain medication.

- Proportion of participants with at least 1-point (2, or 3) reduction in average daily pelvic pain score (cyclic and non-cyclic, combined and separately) as compared to baseline during TRC2, no increase in the average daily use of rescue medication by number of tablets, and no use of concomitant pain medication for ERP.

The following PRO exploratory endpoints will be analyzed using available data.

- Endometriosis Health Profile (EHP)-5:

  The EHP-5 is an endometriosis-specific questionnaire to assess the participant's health-related quality of life. Participants will respond by selecting one of these five categorical responses- "never", "rarely", "sometimes", "often", "always"-" at the beginning of the run-in period (Visit 3) and at the end of TRC 2 (Visit 6) on 5 items from the core questionnaire. The EHP-5 responses will be summarized in terms of frequencies and percentages in the cross-classification table for each of 5 items.

- The Patient's Global Impression of Change (PGIC) ratings:

  The PGIC is a 7-point scale collecting a participant's rating of overall change in her ERP relative to her condition before initiation of the treatment. Participants rate their change as "much better", "better", "a little better", "the same," "a little worse", "worse", or "much worse". Proportion of subjects with improvements (either "much better" or "better" or "a little better" on the PGIC scale) at TRC2 will be analyzed using the stratified Miettinen and Nurminen method (1985) [1].

- Impact score of pelvic pain:

  Fraction of days with no impact (score=0) of endometriosis-related pain (ERP) during BC and TRC2 will be summarized on each of work/school, physical activities, leisure/social activities, and sleep items.

Additionally, change from baseline in average daily pelvic pain score (cyclic and non-cyclic, combined and separately) during TRC2 on days with rescue medication versus days without use rescue medication will also be summarized.

Handling of Missing Data

Sensitivity analyses will be conducted to incorporate methods for handling missing data (i.e., no eDiary entry for either TRC1 or TRC2). The missing data will be imputed based on jump-to-reference method, that is, the missing scores after dropout time in treatment group will be imputed from the placebo group.

The longitudinal data analysis (LDA) method assumes that data are missing at random (MAR). In this study, it is expected that missing at random and missing completely at random (MAR/MCAR) mechanisms will underlie most of the missingness, and the proportion of data missing not at random (MNAR), driven solely by unobserved values of the

study endpoints, will be small. The multiple imputation (MI) approach will be used to assess the robustness of the primary analysis approaches.

Jump-to-reference (J2R) Multiple-imputation Analysis

J2R imputation falls under the category of pattern mixture models known as reference-based imputation (RBI). The RBI approach uses different imputation models for missing data in different treatment groups. In J2R, missing data in the control group are imputed under the MAR assumption, while missing data in the treatment groups are imputed under a MNAR assumption using the control group profile for time points after withdrawal.

The following steps will be used to implement the J2R multiple-imputation analysis.

1) A parameter-estimation model is fitted using PROC MCMC. All of the covariates included in the primary analysis will be used for the parameter-estimation model. For the MCMC procedure, an initial random seed = 72642730 will be used. N = 500 sets pseudo-independent samples of the model parameters will be drawn from the joint posterior distribution.
2) The imputation model is built, where, for each pattern of withdrawal, a predicted value model is created using the parameters estimated in Step 1. The random seed for the imputations is 72642730. For subjects in the control (reference) group, the predicted means are calculated under MAR assumption; for subjects in the other treatment arm, the predicted means are calculated under MNAR using the jump-to-reference approach, that is, the mean profile is based on the same treatment arm before withdrawal and 'jumps' to the mean profile based on the reference arm after withdrawal. A complete dataset will be generated using the imputation model for each set of the N = 500 parameters obtained in Step 1.
3) For each of the imputed complete datasets, an ANCOVA model will be used for the change from baseline values at last time point. The model will include the same covariates as in the primary analysis model. The treatment difference across the 500 datasets will then be combined using PROC MIANALYZE, i.e., using Rubin's rule for multiple imputation (Rubin, 1987) to provide the final results.

To get correct the variance for the jump-to-reference imputation method, a pattern mixture model approximation will also be used. Based on the definition, the jump-to-reference imputation will have a mean treatment difference of zero between treatment and control for those who dropped out in the treatment arm. Therefore, the overall mean treatment difference for jump-to-reference becomes

$$\theta^{J2R} = (\pi_t \mu_t^d + (1-\pi_t)\mu_t^p) - \mu_t^p = \pi_t(\mu_t^d - \mu_t^p)$$

where π_t is the proportion of completers (i.e., subjects with non-missing response at t) in the drug group, t is the last time point, and μ_t^d and μ_t^p are the mean effects for drug and control, respectively. It can be estimated from the primary analysis model as $\hat{\theta}^{J2R} = \hat{\pi}_t(\hat{\mu}_t^d - \hat{\mu}_t^p)$. The variance can be approximated by,

$$\mathrm{var}\left(\hat{\theta}^{J2R}\right) = \hat{\pi}_t^2 \mathrm{var}(\hat{\mu}_t^d - \hat{\mu}_t^p) + \left(\hat{\mu}_t^d - \hat{\mu}_t^p\right)^2 \hat{\pi}_t(1-\hat{\pi}_t)/n$$

where n is sample size in the drug treatment arm. The first term can be estimated from the primary analysis model.

3.6.2 Statistical Methods for Safety Analyses

The APaT population will be used for all safety analyses. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory values, vital signs, and body weight.

The analysis of safety results will follow a tiered approach (Table 2). The tiers differ with respect to the analyses that will be performed. Tier 1 safety endpoints will be subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-group comparisons. Tier 2 safety endpoints will be evaluated via point estimates and 95% CIs for between-group comparisons. Tier 3 safety endpoints will be evaluated via point estimates only.

Tier 1 Events

Safety parameters or adverse events of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals to be provided for between-treatment differences in the proportion of participants with events; these analyses will be performed using the Miettinen and Nurminen (M&N) method (1985), an unconditional, asymptotic method. For this protocol, Taste-related AEs (including dysgeusia, ageusia, and hypogeusia, as well as other related terms) are considered Tier 1 events.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for differences in the proportion of participants with events (also via the M&N method (1985).

Membership in Tier 2 requires that at least 4 participants in any treatment group exhibit the event. The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals for Tier 2 events may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse events and safety parameters that meet predefined limits of change.

In addition to individual events that occur in 4 or more participants in any treatment group, the broad AE categories consisting of the proportion of participants with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, and discontinuation due to an AE will be considered Tier 2 endpoints.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Table 2 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Taste related AE (including dysgeusia, ageusia, and hypogeusia)	X	X	X
Tier 2	Any AE		X	X
	Any Serious AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Any discontinuation due to AE		X	X
	Any discontinuation due to Serious AE		X	X
	Any discontinuation due to Drug-Related AE		X	X
	Any discontinuation due to Serious Drug-Related AE		X	X
	Specific AEs (incidence ≥ 4 participants in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs, or PDLCs [1] (incidence < 4 participants in both treatment groups)			X
	Change from Baseline Results (Lab data, Vital Signs and Body Weight)			X

[1] Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier-2 endpoints.
Note: AE = Adverse Event; SOC=System Organ Class; PDLC=predefined limit of change; X = results will be provided.

The safety lab parameters, vital signs, height and weight will be analyzed based on available data during 5 periods defined as below:

- Screening Period:
  - Starts at the time the subject signs the ICF (Visit 1) and ends the last bleeding day of the SC.
- Run-In Period:
  - Starts on the first non-bleeding day of the BC (i.e. 1 day after the last bleeding day of the SC) and ends prior to the time of witnessed dose on Day 1.
- TRC1 after randomization:
  - Starts on Day 1 at the time of witnessed dose and ends the last bleeding day of TRC1.
- TRC2:
  - Starts on the first non-bleeding day of TRC2 (i.e.1 day after the last bleeding day of the TRC1), and ends the last bleeding day of TRC2 or on the day of last dose of study medication, whichever is last.

- PTC after the participant has stopped taking study intervention:
    - Starts on the first non-bleeding day of PTC (i.e.1 day after the last bleeding day of the TRC 2) or the day after the last dose of study medication, whichever is last and ends on the day of Visit 7.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory, vital signs, and body weights, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

3.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the summary statistics. No statistical hypothesis tests will be performed on these characteristics.

Demographics and baseline characteristics include age, race, ethnicity, body weight, height, BMI (weight/height^2 in kg/m^2), medical history, gynecological history, and prior and concomitant medications. All variables will be summarized by treatment group either by descriptive statistics or categorical tables.

The number and percentage of participants screened and randomized, the primary reasons for screening failure, and the primary reasons for discontinuation will be tabulated. The number of participants who were treated and completed the clinical trial will also be tabulated.

3.7 INTERIM ANALYSES

Treatment-level results and/or participant-level data from the interim analysis will be provided by the unblinded statistician to the standing internal Data Monitoring Committee (siDMC) which consists of SPONSOR personnel. Limited additional SPONSOR personnel may be unblinded to the treatment level results of the interim analysis, if required, in order to act on the recommendations of the siDMC. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician.

The processes by which recommendations and decisions are reached and communicated are documented in the siDMC charter for the SPONSOR**.** The protocol-specific siDMC charter will be referenced in the CSR. Prior to final study unblinding, individuals who have been unblinded at any level will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

This study is planned to have one interim analysis for futility and a final analysis. The interim analysis will be planned for the primary endpoint when 84 participants have been enrolled and completed TRC2 (60% of the participants who are expected to complete TRC2). The Completer Population (see Section 3.5.1) will be used for the assessment of evidence for futility. A non-binding futility criterion will be used based on the futility boundary using

O'Brien-Fleming like beta error spending function (Hwang, Shih, deCani gamma = -4). This is a conservative approach which will spend 2.8% beta error (Type II error) at the IA and the results will be reviewed by the SiDMC. During the futility analysis the enrollment of participants will continue.

At the IA, if the one-sided p-value is ≥ 0.340, which is equivalent to observing that the treatment difference (MK-7264 - placebo) in change from baseline in average daily pelvic pain scores during TRC2 is greater than -0.180 point (Table 3), the study enrollment may be terminated in support of an overall conclusion of futility. The criterion and the boundary properties for the IA are given in Table 3.

Table 3 Boundary Properties for Planned Interim Analysis

Analysis	Value	Futility
IA: 84‡ participants or 60% of the participants who are expected to complete TRC2	Z	-0.413
	Nominal p-value	0.340
	delta at bound§§	-0.180
	P(Cross) if delta=0§	0.660
	P(Cross) if delta=-1#	0.030

‡ The number of 84 participants is 60% of the 140 participants who are expected to complete TRC2, which can provide power 84% for this study.
§§ The difference in change from baseline between MK-7264 and placebo.
§ The probability of crossing the futility bound when the true difference is 0 (null hypothesis).
# The probability of crossing the futility bound when the true difference is -1 (assumed true difference for power calculation).

No Interim analyses for safety will be planned for this protocol.

3.8 MULTIPLICITY

No adjustment will be made for multiplicity

3.9 SAMPLE SIZE AND POWER CALCULATIONS

166 participants (83 in each group) will be randomized in this study, and the expected drop-out rate is 15%. Then 140 evaluable participants (70 participants in each group) will provide 84% power to detect a difference of 1 point between MK-7264 and placebo during TRC2, in change from baseline of the average daily pelvic pain score in the NRS, with one IA conducted when 84 participants have been enrolled and completed TRC2 or 60% of the participants who are expected to complete TRC2. This power calculation is based on a two-sided test with Type I error 0.05. The drop-out rate is from previous trials in chronic cough of MK-7264, and there is limited data to estimate the drop-out rate for ERP. Table 4 provides the power calculations for different assumptions of drop-out rate with the randomized participants.

Table 4 Power Calculation Based on Different Dropout Rates

Number of Randomized Participants	Dropout Rate	Number of Evaluable Participants	Power
166	10%	149	86%
	12%	146	85%
	15% (expected)	140	84%
	20%	132	82%

The assumption of the 1 point difference between MK-7264 and placebo, and the common standard deviation (SD) of 2 units are based on a publication by Diamond [2]. Table 5 provides the power calculations for different assumptions of SD with the sample size.

Table 5 Power Calculation for Different Assumptions of SD with 140 Evaluable Subjects

Difference	SD	power
1	2.5	66%
1	2	84%
1	1.5	98%
1	1	100%

3.10 SUBGROUP ANALYSES AND EFFECT OF BASELINE FACTORS

Analysis for the primary and secondary efficacy endpoints will be provided for the following subgroups of baseline factors:

- Age category (18 – 30, 31 – 49 years).
- Pain intensity: NRS in the eDiary moderate (score: ≥ 5 to <8) and severe (score: ≥8) at baseline.
- Geographic region (US versus ex-US)

Additional subgroup analysis will be provided for change from baseline in average daily use of rescue medication by geographic region (US versus ex-US).

3.11 COMPLIANCE (MEDICATION ADHERENCE)

For each participant, percent compliance will be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should Be on Therapy}} \times 100\%$$

A day within the study will be considered an "On-Therapy" day if the participant takes all required medication. When a participant takes less than or more than the required medication on a day, that day is not considered an "On-Therapy" day.

For participants who are followed for the entire study period, the "Number of Days Should be on Therapy" is the number of days from the first scheduled treatment day to the last scheduled treatment day. For participants who discontinue from the study, the "Number of Days Should be on Therapy" is the number of days from the first scheduled treatment day to the last dose day.

Summary statistics will be provided on percent compliance for the APaT population.

3.12 EXTENT OF EXPOSURE

The duration of treatment for each participant will be evaluated by calculating the number of days on therapy. Exposure to study intervention will be summarized using descriptive statistics (ie, mean, SD, median, minimum, and maximum) for the APaT population.

4. REFERENCES

[1] Miettinen O, Nurminen M. Comparative analysis of two rates. Statistics in Medicine 1985;4:213-26. 03P76P

[2] Diamond MP, Carr B, Dmowski WP, Koltun W, O'Brien C, Jiang P, et al. Elagolix treatment for endometriosis-associated pain: results from a phase 2, randomized, double-blind, placebo-controlled study. Reprod Sci. 2013:1-9. [Epub ahead of print]. 04SJF0