Cover Page for Protocol

Sponsor Name	Ferring Pharmaceuticals Inc.
NCT Number	NCT03692403
Sponsor Trial ID	000165
Official title of study	A randomized, double-blind, placebo-controlled, phase 2 trial assessing the efficacy, safety and dose-response of quinagolide extended-release vaginal rings administered sequentially for 4 menstrual cycles in women with moderate to severe endometriosis-related pain
Document Date	29 May 2020

CLINICAL TRIAL PROTOCOL

A randomized, double-blind, placebo-controlled, phase 2 trial assessing the efficacy, safety and dose-response of quinagolide extended-release vaginal rings administered sequentially for 4 menstrual cycles in women with moderate to severe endometriosis-related pain

RAQUEL
Randomized Trial Assessing Quinagolide Vaginal Ring for Endometriosis-Related Pain

Trial 000165

EudraCT Number:	Not applicable
IND Number:	135,609
Investigational Medicinal Product:	FE 999051, Quinagolide Vaginal Ring
Indication:	Endometriosis-related pain
Phase:	2
Name and Address of Sponsor:	Ferring Pharmaceuticals Inc. 100 Interpace Parkway Parsippany, NJ 07054 United States [redacted]
GCP Statement:	This trial will be performed in compliance with GCP.

SYNOPSIS

TITLE OF TRIAL

A randomized, double-blind, placebo-controlled, phase 2 trial assessing the efficacy, safety and dose-response of quinagolide extended-release vaginal rings administered sequentially for 4 menstrual cycles in women with moderate to severe endometriosis-related pain

SIGNATORY INVESTIGATOR

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TRIAL SITES

Approximately 100 sites in North America

PLANNED TRIAL PERIOD		**CLINICAL PHASE**
Estimated first patient first visit (FPFV):	Q3 2018	2
Estimated last patient last visit (LPLV):	Q3 2022	

BACKGROUND AND SCIENTIFIC JUSTIFICATION FOR CONDUCTING THE TRIAL

Endometriosis is an estrogen-dependent disease, pathologically characterized by the presence of endometrial-like tissue abnormally implanted outside the uterus and primarily located on the pelvic peritoneum, ovaries, and rectovaginal septum. Symptoms of endometriosis often present as pain associated with menstruation (dysmenorrhea), non-menstrual pelvic pain, and pain during or after intercourse (dyspareunia).

As a novel non-hormonal approach to the management of endometriosis, dopamine receptor agonists have been suggested to inhibit the angiogenesis process that is essential for the development and maintenance of endometriotic lesions. Quinagolide is a non-ergot-derived, potent and selective dopamine receptor 2 agonist, which has been formulated into an extended-release vaginal ring for the treatment of endometriosis-related pain.

Non-clinical and clinical data have suggested evidence of the primary pharmacological effects of quinagolide in reduction of endometriotic lesions. In mice with induced endometriosis, a significant reduction in the size of active lesions, cellular proliferation index and angiogenic gene expression was observed with oral quinagolide (50 or 200 µg/kg per day during a 14-day period) versus vehicle. In a proof-of-concept study involving hyperprolactinemic patients with endometriosis, it was observed at second-look laparoscopy that oral administration of quinagolide 25 µg to 75 µg once daily for 18-20 weeks induced a significant reduction in the overall size of endometriotic lesions, in addition to histological evidence of tissue degeneration and down-regulation of vascular endothelial growth factors (VEGF) and proangiogenic cytokines.

Intravaginal administration of quinagolide is well tolerated and has been shown to be associated with higher bioavailability than oral administration due to reduced first-pass metabolism. Single administration of quinagolide vaginal ring demonstrated a pharmacokinetic (PK) profile of T_{max} at 36-48 hours and slowly declining plasma concentration over time for up to 35 days. No dose accumulation was observed following sequential administration of quinagolide vaginal ring for two menstrual cycles.

OBJECTIVES

Primary Objective

- To evaluate the efficacy of three doses of quinagolide administered as an extended-release vaginal ring compared to placebo on reduction of moderate to severe endometriosis-related pain

Secondary Objectives

- To evaluate the effect of quinagolide vaginal ring on reduction of endometriosis-related dysmenorrhea, non-menstrual pelvic pain, dyspareunia and analgesic use
- To evaluate the effect of quinagolide vaginal ring on the subject's ability to function
- To evaluate the effect of quinagolide vaginal ring on ovarian function
- To evaluate the effect of quinagolide vaginal ring on endocrine parameters
- To evaluate the effect of quinagolide vaginal ring on vaginal bleeding pattern
- To evaluate the systemic exposure of quinagolide and metabolites after quinagolide vaginal ring administration
- To evaluate the effect of quinagolide vaginal ring on bone turnover markers
- To evaluate the safety profile of quinagolide vaginal ring including adverse events, symptoms of impulse control disorders, electrocardiography (ECG) and echocardiography findings, routine safety laboratory parameters and ring acceptability
- To validate the newly developed patient reported outcome (PRO) tool: Women's Endometriosis Diary [Note: This objective will be reported separately]

Exploratory Objective

- To explore the effect of quinagolide vaginal ring on endometriosis biomarkers such as angiogenic and inflammatory biomarkers

ENDPOINTS

Primary Endpoint

- Changes in the mean daily Numerical Rating Scale (NRS) scores for the worst endometriosis-related pain at cycle 4

Secondary Endpoints

- Changes in the mean daily NRS scores for the worst endometriosis-related pain on days with menstrual bleeding (i.e. dysmenorrhea) and for the worst endometriosis-related pain on days with no menstrual bleeding (i.e. non-menstrual pelvic pain) at cycle 4
- Changes in the mean daily NRS scores for the worst endometriosis-related pain over 4 menstrual cycles
- Changes in the mean daily NRS scores for the worst dysmenorrhea over 4 menstrual cycles
- Changes in the mean daily NRS scores for the worst non-menstrual pelvic pain over 4 menstrual cycles

- Changes in the mean daily NRS scores for the worst dyspareunia on days with sexual intercourse over 4 menstrual cycles
- Frequency of avoiding sexual intercourse due to expected pain over 4 menstrual cycles
- Changes in the mean daily NRS scores for the worst impact of endometriosis-related pain on the subject's ability to function over 4 menstrual cycles
- Changes in the mean weekly scores of the Endometriosis Health Profile-30 (EHP-30) pain impact domain over 4 menstrual cycles
- Changes in vaginal bleeding pattern over 4 menstrual cycles
- Percentage of days with mild and/or strong rescue analgesics used over 4 menstrual cycles
- Total and average doses of mild and/or strong rescue analgesics used over 4 menstrual cycles
- Responder rate assessed as ⩾30%, ⩾50% and ⩾70% reduction from the baseline in mean daily NRS score for the worst endometriosis-related pain, dysmenorrhea and non-menstrual pelvic pain and for the worst endometriosis-related pain impact, over 4 menstrual cycles
- Changes in the mean individual and total symptom and sign severity scores of the Biberoglu and Behrman (B&B) scale at cycle 4
- Changes in the EHP-30 scores over 4 menstrual cycles
- Changes in Patient Global Impression of Severity (PGIS) scores at cycle 4
- Patient Global Impression of Change (PGIC) scores at cycle 4
- Plasma concentration of quinagolide and metabolites during cycles 1 and 4
- Serum levels of mid-luteal phase progesterone at cycle 4
- Proportion of subjects with serum levels of mid-luteal progesterone ⩾25 nmol/L (7.9 ng/mL) at cycle 4
- Serum levels of mid-luteal estradiol, prolactin, thyroid-stimulating hormone (TSH) and insulin-like growth factor-1 (IGF-1) at cycle 4
- Changes in bone turnover markers, determined by bone resorption marker serum C-terminal cross-linking telopeptide of type 1 collagen (s-CTx) and bone formation marker serum procollagen type I N propeptide (s-PINP) at cycle 4
- Changes in ECG parameters including PR interval, QT interval, corrected QT using Fridericia's formula (QTcF) and QRS interval at cycle 4
- Proportion of subjects with abnormal clinically significant echocardiography findings indicating valvular heart disease at cycle 4
- Proportion of subjects identified with potential impulse control disorders by the questionnaire for impulsive-compulsive disorders at cycle 4
- Frequency and intensity of adverse events
- Changes in circulating levels of clinical chemistry and hematology parameters, urinalysis parameters, and proportion of subjects with markedly abnormal changes
- Frequency and intensity of ring acceptability parameters over 4 menstrual cycles

Exploratory Endpoint

- Changes in endometriosis biomarkers such as serum levels of VEGF, placenta growth factor (PlGF), interleukin 6 (IL-6) and soluble fms-like tyrosine kinase 1 (sFlt-1) at cycle 4

METHODOLOGY

This is a randomized, double-blind, placebo-controlled, phase 2 trial assessing the efficacy, safety and dose-response of quinagolide extended-release vaginal rings administered sequentially for 4 menstrual cycles in women with moderate to severe endometriosis-related pain. In this trial, a menstrual cycle is considered the period from day 7 of return of menses (RM+7) in a cycle until the following day 7 of return of menses in the next cycle. Visits on RM+7 can be scheduled on RM+6-10, i.e. day 6 to day 10 of return of menses.

The trial consists of the following periods:

1) Screening: starting immediately after the signing of the informed consent(s) and including a run-in period of two complete menstrual cycles (cycles -2 and -1)
2) Treatment: double-blind, placebo-controlled treatment with three doses of quinagolide extended-release vaginal ring administered sequentially for four menstrual cycles (cycles 1, 2, 3 and 4)
3) Follow-up: post-treatment follow-up period of one menstrual cycle (cycle 5)

Screening: The screening period includes a wash-out period of approximately one month (only applicable to subjects currently using some hormonal products such as contraceptives) and a run-in period of two complete menstrual cycles (cycles -2 and -1, applicable to all subjects). Subjects who are currently using some hormonal products such as contraceptives, may be eligible for the trial if they have completed the wash-out period. In this case, subjects need to sign the informed consent(s) before they discontinue those products. Discontinuation of the products should follow the labelling (e.g. completing the current cycle of contraceptives before wash-out). Subjects requiring wash-out will not be provided with the electronic diary (e-Diary) or rescue analgesics until the completion of the wash-out period, i.e. at the run-in visit.

Before entry into run-in, all subjects will be asked to score the worst endometriosis-related pain from a recall of their experience during the past menstrual cycle on a self-administered 11-point Numerical Rating Scale (NRS) with 0 indicating “no pain” and 10 indicating “worst imaginable pain”. After standardized training of e-Diary use, eligible subjects will be instructed to record endometriosis-related pain, vaginal bleeding, occurrence of sexual intercourse and analgesic use in the e-Diary on a daily basis. Impact of endometriosis-related pain on functioning will be assessed by subjects on both a daily and a weekly basis.

In this trial, endometriosis-related pain is evaluated as the pain located in the abdominal-pelvic area and the lower back area. During the run-in period, subjects will score the worst endometriosis-related pain during the preceding 24 hours on the NRS before bedtime every night in the e-Diary.

Vaginal bleeding will be recorded as “yes” or “no” on a daily basis in the e-Diary. If there is vaginal bleeding, subjects will be asked to register their bleeding volume (spotting, light, moderate or heavy bleeding) and to answer whether they think the bleeding is related to menses or not. Based on the subject’s impression of whether she has menstrual bleeding or not, the NRS score obtained for the endometriosis-related pain is assigned to dysmenorrhea (endometriosis-related pain on days with menstrual bleeding) or to non-menstrual pelvic pain (endometriosis-related pain on days with no menstrual bleeding).

Occurrence of sexual intercourse (“yes” or “no”) will also be recorded in the e-Diary. In case of sexual intercourse, subjects will be asked to score the worst pain experienced during or after

intercourse (dyspareunia) on the NRS. In case of no sexual intercourse, subjects will be asked if it is due to expected pain.

Rescue analgesics for endometriosis-related pain will be limited to ibuprofen and/or hydrocodone-acetaminophen in this trial. As a mild analgesic, ibuprofen will be provided to subjects in the form of 200 mg oral tablets for their use on an as-needed basis. Subjects will be instructed not to use other analgesics unless necessary. If there is a need to change analgesics, subjects should discuss with investigators, who may prescribe a strong analgesic, i.e. 5 mg hydrocodone plus 300 mg or 325 mg acetaminophen. Use of any other analgesics for endometriosis-related pain is prohibited. Any prophylactic use of analgesics is also prohibited in this trial. Use of analgesics for endometriosis-related pain will be reported by subjects in the e-Diary on a daily basis.

The impact of the endometriosis-related pain on different aspects of functioning will be assessed by subjects both on the NRS on a daily basis and by the modified EHP-30 pain impact domain (i.e. the first 11 items plus an additional work item) on a weekly basis.

Treatment: Subjects will be randomized on RM+7 of cycle -1 (at visit 4) if they, during the run-in period, have moderate to severe endometriosis-related pain, which is defined as having a mean daily NRS score of ≥4 for the worst endometriosis-related pain during each run-in menstrual cycle. Randomization will be performed in a 1:1:1:1 ratio to quinagolide vaginal ring dose load 360 µg at a target release rate of quinagolide 4.5 µg/day, quinagolide vaginal ring dose load 720 µg at a target release rate of quinagolide 9 µg/day, quinagolide vaginal ring dose load 1080 µg at a target release rate of quinagolide 13.5 µg/day or placebo vaginal ring for four menstrual cycles (cycles 1, 2, 3 and 4).

Follow-up: Subjects will be followed up for one menstrual cycle (cycle 5).

From randomization to follow-up (cycle 1 to cycle 5), subjects will continue to use an e-Diary to score the endometriosis-related pain, to register vaginal bleeding pattern, occurrence of sexual intercourse and the analgesic use as well as to assess the impact of the worst endometriosis-related pain on functioning, as they have done in the run-in period.

During the treatment period, subjects will self-insert the assigned ring in the upper part of the vagina on RM+7 of cycle 1 to cycle 4 at the clinic by following standard instructions for use. Supervision by the site staff can be provided if needed. After insertion, the vaginal ring will be kept in the vagina continuously for one menstrual cycle until being replaced with the next ring on RM+7 of the next cycle when the subject visits the clinic. Acceptability of the ring will be assessed by subjects via a ring acceptability questionnaire at each RM+7 visit during the treatment period. Unless under other effective birth control permitted by protocol, subjects will be required to use a non-hormonal single-barrier contraception (i.e. condom) from wash-out (if applicable) or run-in to end-of-trial. Contraception counselling and condoms will be offered to subjects throughout the trial.

B&B will be administered electronically at randomization and at cycle 4 (at visits 4 and 10), with trained trial coordinators completing the first part based on subjects' verbal responses and investigators completing the second part based on findings of a pelvic examination. Subjects will complete the electronic version of the EHP-30 questionnaire at randomization, and at every cycle from cycle 1 to cycle 4 (at visits 4, 6, 7, 8 and 10). PGIS scale will be completed electronically by subjects at cycle -2, at randomization and at cycle 4 (at visits 2, 4 and 10), while PGIC scale will be completed electronically at cycle 4 (at visit 10).

Blood samples will be collected throughout the trial for the purpose of evaluating mid-luteal phase endocrine parameters, bone turnover markers, endometriosis biomarkers, quinagolide and metabolites, and routine safety laboratory parameters. In this trial, mid-luteal phase is defined as 6-9 days after luteinizing hormone (LH) surge (LH+6-9) as tested by subjects at home by means of commercially available urinary LH kits. LH+7 visits can be scheduled on LH+6-9, either based on an actual LH surge date as indicated by a positive LH surge test or based on an estimated LH surge date according to subjects' cycle length if subjects fail to detect the LH surge. The exact cycle day of the LH+7 visit will be derived based on the first menstrual bleeding date of the current cycle confirmed at the RM+7 visits. An endocrine panel including estradiol, progesterone, prolactin, TSH and IGF-1 will be assessed during the mid-luteal phase of cycles -1 and 4 (at visits 3 and 9). Evidence of ovulation will be evaluated by serum levels of mid-luteal progesterone. Fasting blood samples for the analysis of a bone formation marker (s-PINP) and a bone resorption marker (s-CTx) will be collected during cycles -1 and 4 (at visits 3 and 9). Blood samples for endometriosis biomarkers including, but not limited to, VEGF, PlGF, IL-6 and sFlt-1 will also be collected during cycles -1 and 4 (at visits 3 and 9). At the same time points, if subjects have provided a separate informed consent, additional blood samples for potential analyses of circulating cell-free DNA and microRNA will also be collected. Routine safety laboratory tests for clinical chemistry and hematology parameters will be performed during cycle -1, at end-of-treatment and end-of-trial (at visits 3, 10 and 11). Quinagolide and metabolites will be measured within 1-5 days of first ring insertion, at RM+7 visits of cycles 1, 3 and 4 as well as at LH+7 visit of cycle 4 (at visits 5, 6, 8, 9 and 10) to assess systemic exposure and allow for population PK modelling. Blood samples should be taken prior to ring removal at RM+7 visits. If subjects have provided a separate informed consent, a blood sample for pharmacogenetic analysis will also be collected at visit 5.

ECG and echocardiography will be performed at screening and at end-of-treatment to monitor cardiovascular safety. ECG and echocardiography at screening can be arranged anytime during cycle -1 e.g. at LH+7 visit (visit 3) but results must be available prior to randomization. ECG and echocardiography at cycle 4 can be performed within ±2 weeks of visit 10.

A modified questionnaire for impulsive-compulsive disorders (QICD) will be completed electronically by trained trial coordinators based on subjects' verbal response prior to randomization at cycles -1 and 4 (at visits 4 and 10).

A urine pregnancy test will be performed at each clinic visit (except for visit 5) throughout the trial. If the test result is positive and is confirmed by a following serum βhCG test, the subject should be discontinued from the trial. Urinalysis is performed before entry into run-in (before or at visit 1) and at cycle 4 (at visit 10).

All subjects will be asked which treatment they believe they have received at the end of treatment. A sub-group of 60 subjects including 5 non-completers from selected sites, if they have provided a separate informed consent, will be invited to participate in a patient interview at the end of treatment to help determine the meaningful treatment benefit from the patients' perspective and to assess the content validity of the questions related to daily functioning in the e-Diary.

An internal Clinical Monitoring Committee consisting of the responsible medical officer, statistician and clinical trial manager will be established to regularly review the trial data including data with respect to the pre-defined stopping criteria in a blinded manner. An independent Data Monitoring Committee (DMC) consisting of exclusively external members will also be established. If the pre-defined stopping criteria on the treatment group or trial level are met, the DMC will be

requested to access unblinded safety data presented by treatment group and will recommend whether one dose, several doses or the trial should be discontinued. The DMC will also have access to the unblinded interim data presented by treatment group and will recommend whether the trial should be stopped for futility. In any case, the DMC will keep the data and analyses confidential from any persons involved in the conduct of the trial.

An interim analysis is planned when approximately half of the planned evaluable subjects (104 subjects) have completed the treatment period of the trial for the assessment of the primary endpoint. The data will be prepared by treatment group by an external statistician. The purpose of the interim analysis is to evaluate futility of the trial and to adjust sample size if needed.

NUMBER OF SUBJECTS

It is planned to screen around 590 subjects to randomize 280 subjects (70 subjects per treatment group) to achieve 208 evaluable subjects at the end of treatment. The sample size will be re-estimated by an external statistician during an interim analysis and the number of randomized subjects may be adjusted up to 360.

CRITERIA FOR INCLUSION / EXCLUSION

Inclusion Criteria

1. Informed consent(s) signed and dated prior to screening evaluations.
2. Pre-menopausal females aged ≥18 years at time of signing informed consent(s).
3. Body mass index (BMI) of 18-42 kg/m^2 (both inclusive) at screening.
4. Documentation of diagnosis by surgical visualization of endometriosis (laparoscopy or laparotomy) within the last 10 years before the run-in visit or visualization of persistent endometrioma (≥2 cm in diameter) by repeat ultrasound in two separate menstrual cycles before subject's entry into run-in.
5. Willing and able to use a non-hormonal single-barrier contraception (i.e. condom) from wash-out (if applicable) or run-in to the end-of-trial. This is not required if adequate contraception is achieved by vasectomy of the male sexual partner, surgical sterilization (e.g. tubal ligation and blockage methods such as ESSURE) of the subject, or true abstinence of the subject (sporadic sexual intercourse with men still requires condom use).
6. Willing to avoid the use of vaginal douches or any other intravaginally administered medications or devices from randomization to the end of treatment.
7. Willing to change usual analgesics to rescue analgesics as permitted by protocol for endometriosis-related pain from the start of run-in to the end-of-trial.
8. Willing to avoid any prophylactic use of analgesics from the start of run-in to the end-of-trial.
9. Willing to avoid any change in the use of non-drug therapy (e.g. acupuncture and physiotherapy) for endometriosis-related pain from the start of run-in to the end-of-trial.
10. Transvaginal ultrasound documenting a uterus with no clinically significant abnormalities (e.g. hysterectomy) and presence of at least one ovary with no clinically significant abnormalities with the exception of endometrioma (e.g. no evidence of ovarian cyst ≥5 cm, fibroid ≥4 cm, or presence of a submucosal fibroid) at the run-in visit.

11. Two regular menstrual cycles of 24-35 days (both inclusive) observed during the run-in period.
12. Having moderate to severe endometriosis-related pain defined as:
    12a) At the run-in visit, on a self-administered 11-point NRS, having an NRS score of ≥5 for the worst endometriosis-related pain during the past menstrual cycle.
    12b) At randomization, on the self-administered 11-point NRS, having a mean daily NRS score of ≥4 for the worst endometriosis-related pain during each run-in cycle.
13. Completion of the daily e-Diary for at least 80% of the days on average in two run-in cycles, from the day the e-Diary is available at the start of cycle -2 through the day before visit 4 at the end of cycle -1.
14. Documentation of a normal cervical cytology or negative results of human papilloma virus (HPV) reflex testing within 24 months of the start of run-in. If atypical squamous cells of undetermined significance were present on prior tests, additional follow-up HPV test results should be negative for high-risk viral subtypes.
15. Negative cervical swab for gonorrhea and chlamydia at screening.
16. Willing and able to comply with trial procedures, including filling in the e-Diary in English or Spanish, attending scheduled visits and adherence to treatment plan.

Exclusion Criteria

1. Use of depot medroxyprogesterone acetate (MPA) within 10 months of the start of run-in.
2. Use of gonadotropin releasing hormone (GnRH) agonists (3-month depot injection) or dopamine agonists within 6 months of the start of run-in.
3. Use of GnRH agonists (1-month depot injection or nasal spray) or birth control implants (e.g. NEXPLANON) within 3 months of the start of run-in.
4. Use of GnRH antagonists, aromatase inhibitors, danazol, intrauterine devices or hormonal contraceptives (including combined oral contraceptive pill, progestin-only pill, transdermal patch and contraceptive ring) within 1 month of the start of run-in.
5. Undiagnosed abnormal vaginal bleeding.
6. Current vestibulodynia and vulvodynia.
7. Chronic abdominal, pelvic or lower back pain diagnosed to be of non-endometriosis origin (e.g. presumptive adenomyosis as a dominant condition diagnosed by magnetic resonance imaging (MRI) or ultrasound, inflammatory bowel disease, interstitial cystitis, spinal disc herniation) that would interfere with the assessment of endometriosis-related pain.
8. Current diagnosis of a chronic pain syndrome (e.g. fibromyalgia, chronic back pain, myofascial pain syndrome, chronic headache) or any other condition that requires continuous use of analgesic therapy.
9. Known bone diseases (e.g. osteoporosis, Paget's disease and osteomalacia) affecting bone resorption or bone formation markers.
10. Chronic endocrine abnormality affecting the hypothalamic-pituitary-gonadal axis or leading to ovarian dysfunction except for hyperprolactinemia.
11. Known positive results of hepatitis B virus, hepatitis C virus and human immunodeficiency virus (HIV) antibody tests.
12. History of no relief of endometriosis-related pain after any medical therapy or surgery.

However, history of partial pain relief, discontinuation due to side effects from medical therapy or non-adherence to post-surgery medical therapy are not exclusionary.

13. History of having used more than 2 consecutive weeks of a prohibited long-acting narcotic or immediate-release narcotic for treatment of endometriosis-related pain within 6 months of the start of run-in.
14. History of malignancy within 5 years of the start of screening, except for adequately managed basal cell carcinoma and squamous cell carcinoma of the skin.
15. History of recurrent bacterial / fungal vaginal infection or recurrent urinary tract infection (all defined as ≥4 episodes within a year).
16. History of orthostatic hypotension or recurrent syncope.
17. History of mental illness including occurrence of acute psychosis, bipolar disorders and schizophrenia (except for well-controlled anxiety and/or depression with no changes to interventions for 6 months prior to start of run-in).
18. History of impulse control disorders including pathological gambling, compulsive buying, hypersexuality, and binge eating or being identified with potential impulse control disorder by the questionnaire for impulsive-compulsive disorders (a score ≥2 for any sub-questions of Question 3 or a score ≥1 for any sub-questions of Question 4) prior to randomization.
19. History of valvular heart disease.
20. History of sudden sleep onset episodes.
21. Any clinically significant abnormal findings from vital signs, urinalysis, blood tests of hematology and clinical chemistry at screening, including a drop of 20 mmHg of systolic blood pressure or a drop of 10 mmHg of diastolic blood pressure within three minutes of standing from a sitting position, alanine aminotransferase (ALT) >2.5 times upper limit of normal (ULN) or bilirubin >1.5 times ULN or creatinine >1.5 mg/dL.
22. Any clinically significant abnormal findings from blood test of endocrine parameters (including signs indicating menopausal status but excluding hyperprolactinemia) at screening.
23. Any clinically significant abnormal findings from physical examination at screening.
24. Any vaginal or vulvar lesions that could interfere with vaginal ring usage.
25. Any significant abnormal ECG or echocardiography findings (e.g. valvular regurgitation or stenosis) before randomization.
26. Any recent suicidal ideation of type 4 (i.e. active suicidal ideation with some intent to act, without specific plan) or type 5 (i.e. active suicidal ideation with specific plan and intent), or suicidal behavior identified by the electronic Columbia-Suicide Severity Rating Scale at screening.
27. Hypersensitivity to any active ingredient, excipients or other component of medicinal products used in the trial, including quinagolide vaginal ring, placebo vaginal ring and ibuprofen.
28. Known serious adverse drug reactions to dopamine agonist.
29. Current or history of gastrointestinal ulcer or gastrointestinal bleeding within 6 months of the run-in visit.
30. Current pregnancy as confirmed by a positive serum βhCG test at screening or planning a

pregnancy within the duration of the trial, currently breast-feeding or less than 6 months post-partum of the run-in visit.

31. Planned surgical treatment of endometriosis or planned surgery in the abdominal-pelvic or lower back area within the duration of the trial that could interfere with the efficacy assessment.
32. History of drug abuse within 2 years of the start of screening or a current positive urine drug screen, unless the cause of the positive result is from opioids and antidepressants that are medically indicated and prescribed by a physician.
33. Current or history of alcohol abuse within 2 years of the start of the run-in visit.
34. Current or previous participation in a clinical trial involving a non-registered investigational medicinal product within 1 month of the run-in visit. If the trial involves a hormonal drug, the exclusion criteria 1-4 shall apply.

INVESTIGATIONAL MEDICINAL PRODUCTS

Quinagolide vaginal ring is an extended-release system with a dose load of quinagolide 360 µg, 720 µg and 1080 µg at a target daily release rate of quinagolide 4.5 µg/day, 9 µg/day and 13.5 µg/day, respectively, for up to 35 days duration.

- Quinagolide vaginal ring dose load 360 µg at a target release rate of quinagolide 4.5 µg/day: administered once per menstrual cycle (up to 35 days), sequentially for four menstrual cycles
- Quinagolide vaginal ring dose load 720 µg at a target release rate of quinagolide 9 µg/day: administered once per menstrual cycle (up to 35 days), sequentially for four menstrual cycles
- Quinagolide vaginal ring dose load 1080 µg at a target release rate of quinagolide 13.5 µg/day: administered once per menstrual cycle (up to 35 days), sequentially for four menstrual cycles
- Placebo vaginal ring: administered once per menstrual cycle (up to 35 days), sequentially for four menstrual cycles

DURATION OF TREATMENT

Subjects will be exposed to placebo vaginal ring or quinagolide vaginal ring for 4 menstrual cycles, depending on randomization.

STATISTICAL METHODS

Primary Endpoint Analysis

The primary objective of this trial is to evaluate the efficacy of three doses of quinagolide administered as an extended-release vaginal ring compared to placebo on reduction of moderate to severe endometriosis-related pain. The primary endpoint is the change in mean daily NRS score for the worst endometriosis-related pain at cycle 4.

The participating subjects will record their NRS score daily throughout each menstrual cycle. For each cycle the daily recordings will be averaged to calculate the mean daily NRS score. The mean daily NRS score obtained during the two run-in menstrual cycles (cycles -2 and -1) will be considered the baseline mean daily NRS score. The primary endpoint will be derived as the difference between the mean daily NRS score for cycle 4 and the baseline mean daily NRS score.

The primary endpoint will be analyzed using a repeated measures analysis of covariance

(ANCOVA) model, with the change in mean daily NRS score from baseline measured at cycles 1, 2, 3 and 4 as dependent variable, the baseline mean daily NRS score and the baseline percentage of days on rescue analgesics by type as covariates, as well as treatment group and treatment by cycle as fixed effect. Unstructured error-covariance matrices will be used. The treatment contrasts between each active treatment versus placebo at cycle 4 will be reported with 95% confidence intervals and corresponding p-values.

The primary analysis will be based on observed cases in the intention-to-treat (ITT) analysis set, while the analysis based on the per-protocol (PP) population will be considered supportive and serve as one of the sensitivity analyses. Other sensitivity analyses focus, among other things, on:

- the impact of missing data if assuming missing not at random by applying a placebo-based pattern mixture model
- the heterogeneity of the effect in terms of baseline mean daily NRS score, percentage of days on rescue analgesics by type at baseline by testing respective treatment interactions
- the impact of also adjusting the ANCOVA model for the percentage of days on rescue analgesics by type at cycles 1, 2, 3, and 4 (time dependent) and the impact of changing baseline NRS score from a daily mean of two run-in cycles to that of the last run-in cycle

Secondary Endpoint Analysis
Secondary efficacy endpoints are analyzed longitudinally by applying repeated measures ANCOVA for continuous endpoints, repeated measures logistic-regression using the generalized estimating equation (GEE) approach and logit link function for binary data, and repeated measures negative-binomial regression analysis using the GEE approach with log link function for count data. Unstructured error-covariance matrices will be used. In addition, time to first occurrence of response will be analyzed using proportional odds regression. Secondary safety endpoints will be analyzed for the safety analysis set, whereas all other endpoints will be analyzed for both the ITT and PP populations.

Interim Analysis
An interim analysis with the option to stop the trial early due to futility will be performed by an external statistician when approximately half of the planned evaluable subjects (104 subjects) have completed the treatment period of the trial for the assessment of the primary endpoint using unblinded data. The futility bound is set at a conditional power using current trend equal to 5%, i.e. the trial could be potentially stopped for futility if the probability of achieving a significant result in the highest remaining dose group is lower than 5% based on the observed data at the interim analysis. In case of high drop-out rate or discontinuations in the highest dose group, the analysis will be performed on the remaining dose(s). No interim analysis intended to stop the trial early due to overwhelming efficacy is planned.

Sample Size Calculations
The sample size calculation is based on demonstrating superiority of quinagolide vaginal ring compared with placebo vaginal ring on the primary endpoint of change in mean daily NRS score for the endometriosis-related pain at cycle 4.

Assuming that the standard deviation of the change in mean daily NRS is 1.5 units, a sample size of 52 evaluable subjects per group will have at least 90% power to detect a treatment effect difference of 1.0 unit using a t-test at a 5% two-sided significance level in a pre-defined hierarchical step-down procedure starting with testing the highest dose versus placebo, taking into account the planned interim analysis for futility at a conditional power using current trend equal to 5%. Accounting for an approximately 25% drop-out rate, 70 subjects should be randomized to each treatment group, i.e. in total 280 subjects should be randomized. A sample size re-estimation will be performed by the external statistician at the same time of the interim analysis. The sample size may be increased to 360 subjects.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

List of Abbreviations

1-5d	1-5 days
2D	2-dimensional
5-HT	5-hydroxytryptamin receptor
5-HT2B	5-hydroxytryptamin 2B receptor
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical Classification System
AUC_{tau}	area under the plasma concentration-time curve during a dosing interval
B&B	Biberoglu and Behrman
βhCG	beta unit of human chorionic gonadotropin
BMI	body mass index
BOCF	baseline-observation-carried-forward
BTM	bone turnover markers
CBC	complete blood count
C_{max}	maximum plasma concentration
COX2	cyclooxygenase-2
COVID-19	coronavirus disease 2019
CR	controlled-release
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP2D6	cytochrome P450 2D6
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
E2	estradiol
ECG	electrocardiography
Echo	echocardiography
e-CRF	electronic case report form
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
e-Diary	electronic diary
EHP-30	Endometriosis Health Profile-30
EOT	end-of-trial
EOTx	end-of-treatment
ER	extended-release
EudraCT	European Union Clinical Trial Database
FDA	Food and Drug Administration
FPFV	first patient first visit
GCP	Good Clinical Practice
GEE	generalized estimating equation
GMP	Good Manufacturing Practice
GnRH	gonadotropin releasing hormone
Gyn exam	gynecological examination
h	hours
HBV	hepatitis B virus
HCV	hepatitis C virus

HIV	human immunodeficiency virus
HPV	human papilloma virus
ICH	International Conference on Harmonisation
ICH-GCP	International Conference on Harmonisation-Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
IGF-1	insulin-like growth factor-1
IL-6	interleukin 6
IMP	investigational medicinal product
IND	investigational new drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intention-to-treat
kg	kilogram
L	liter
lab	laboratory
LH	luteinizing hormone
LH+6-9	6-9 days after LH surge
LH+7	7 days after LH surge
LOCF	last-observation-carried-forward
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MPA	medroxyprogesterone acetate
MRI	magnetic resonance imaging
NIMP	non-investigational medicinal product
nmol	nanomol
NSAIDs	non-steroidal anti-inflammatory drugs
NRS	Numerical Rating Scale
OHSS	ovarian hyperstimulation syndrome
P4	progesterone
pg	picogram
PG	pharmacogenetic(s)
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PlGF	placenta growth factor
PP	per-protocol
PR interval	the interval between the start of the P wave and the start of the QRS complex, corresponding to the time between onset of atrial depolarization and onset of ventricular depolarization
PRO	patient reported outcome
QICD	Questionnaire for Impulsive-Compulsive Disorder
QRS interval	the interval between the start of Q wave to the end of the S wave, corresponding to ventricle depolarization
QTcF	corrected QT interval using Fridericia's formula

QT interval	the interval between the start of the Q wave and the end of the T wave, corresponding to electrical systole
QVR	quinagolide vaginal ring
RM	return of menses
RM+1	day 1 of return of menses
RM+6-10	day 6 to day 10 of return of menses
RM+7	day 7 of return of menses
RNA	ribonucleic acid
RR interval	the interval from the start of one R wave to the next
SAE	serious adverse event
SAP	statistical analysis plan
s-CTx	serum C-terminal cross-linking telopeptide of type 1 collagen
sFlt-1	soluble fms-like tyrosine kinase-1
SOC	system organ class
s-PINP	serum procollagen type I N propeptide
SUSAR	suspected unexpected serious adverse reaction
T_{max}	time to maximum plasma concentration (C_{max})
TSH	thyroid-stimulating hormone
TVU	transvaginal ultrasound
µg	microgram
ULN	upper limit of normal
V	visit
VEGF	vascular endothelial growth factor

Definition of Terms

Menstrual cycle	In this trial, a menstrual cycle is considered the period between day 7 of return of menses (RM+7) until the following RM+7 in the next cycle. RM+7 visit can be arranged day 6 to day 10 of return of menses. The starting day of return of menses (RM) is day 1 of return of menses (RM+1).
Mid-luteal phase	In this trial, mid-luteal phase is defined as 6-9 days after LH surge (LH+6-9). LH+7 visit can be arranged 6-9 days after LH surge.

Progesterone Units Conversion Factor

1 ng/mL=3. 184 nmol/L
1 nmol/L=0.314 ng/mL

1 INTRODUCTION

1.1 Background

Endometriosis is an estrogen-dependent disease, pathologically characterized by the presence of endometrial-like tissue abnormally implanted outside the uterus and primarily located on the pelvic peritoneum, ovaries, and rectovaginal septum.[1] Symptoms of endometriosis often present as pain associated with menstruation (dysmenorrhea), non-menstrual pelvic pain, and pain during or after intercourse (dyspareunia).[2,3] Endometriosis is estimated to affect 6% to 10% of women of reproductive age and up to 50% of women with infertility.[4,5] Affected women can lose up to 10 working hours weekly, mainly owing to reduced effectiveness whilst working.[6] It has been estimated that, in the United States, the costs of diagnosing endometriosis and treating associated pain and infertility is in excess of $50 billion per annum and yet, treatment options remain inadequate.[7]

Treatment of endometriosis-related pain currently involves repeated courses of medical therapy, surgical therapy, or both. Empirical treatment with analgesics and combined oral contraceptives, without prior definitive diagnosis of endometriosis by laparoscopy, is usually the first line treatment especially in adolescents.[8] Self-administered non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used initially to relieve pain symptoms associated with endometriosis, but the effectiveness is not well established.[3] All established hormonal therapies (progestins, gonadotropin releasing hormone (GnRH) agonists, and danazol) are similarly effective. However, some of these drugs are associated with anti-ovulatory effect leading to amenorrhea and oligomenorrhea or with hypoestrogenic effect such as bone loss and vasomotor symptoms, all of which limit their duration of use and result in undesirable iatrogenic sterility in women seeking conception.[9,10] Long-term treatment of endometriosis without undesirable anti-ovulatory or hypoestrogenic effects remains an unmet medical need.

As a novel non-hormonal approach to the management of endometriosis, dopamine receptor agonists have been suggested to inhibit the angiogenesis process that is essential for the development and maintenance of endometriotic lesions. Non-clinical and clinical data have suggested evidence of the primary pharmacological effects of dopamine receptor agonists in reduction of endometriotic lesions.

Quinagolide is a non-ergot-derived, potent and selective dopamine receptor 2 agonist. Quinagolide is available in some countries outside the United States as oral tablets for the treatment of hyperprolactinemia with extensive post-marketing experience. In addition, it has been formulated into an extended-release vaginal ring for the treatment of endometriosis-related pain. The vaginal ring allows extended release of quinagolide for up to 35 days and can be replaced by a new vaginal ring in every menstrual cycle.

For further information regarding quinagolide vaginal ring, please refer to the Investigator's Brochure.[11]

1.2 Scientific Justification for Conducting the Trial

As an integral part of the endometriosis pathogenesis, the establishment of a new blood supply is essential for survival and growth of endometriotic tissues when implanted outside the uterine cavity. This angiogenesis process is a critical mechanism that allows the development of endometriosis. The most prominently studied angiogenic factor is vascular endothelial growth factor (VEGF), which has been noted in endometriotic lesions, endometriomas and the peritoneal fluid of endometriosis patients.[12,13,14] A positive correlation between the severity of endometriosis and the level of VEGF concentration in peritoneal fluid has been observed.[14]

Dopamine 2 receptors are present in ectopic endometrium.[15] Dopamine agonist-mediated dopamine receptor 2 activation promotes VEGF receptor 2 endocytosis, preventing binding of VEGF to VEGF receptor 2. Administration of dopamine receptor 2 agonists was shown to reduce vascular permeability without affecting corpus luteum angiogenesis and function by partially inhibiting VEGF receptor 2 phosphorylation.[16] In addition, it has been shown that dopamine receptor 2 agonists diminish nerve fibre density in experimental endometriotic lesions.[17]

Non-clinical and clinical data have suggested evidence of primary pharmacological effects of quinagolide in reduction of endometriotic lesions. In mice with induced endometriosis, a significant reduction in the size of active lesions, cellular proliferation index and angiogenic gene expression was observed with oral quinagolide (50 or 200 µg/kg per day during a 14-day period) versus vehicle.[18] In a proof-of-concept clinical trial involving 9 hyperprolactinemic patients with endometriosis, it was observed at second-look laparoscopy that oral administration of quinagolide 25 µg to 75 µg once daily for 18-20 weeks induced a significant reduction in the overall size of endometriotic lesions, together with histological evidence of tissue degeneration and down-regulation of VEGF and proangiogenic cytokines.[19]

Three phase 1 trials have been conducted in Germany and the United Kingdom with intravaginal administration of quinagolide in healthy volunteers. Intravaginal administration of quinagolide tablets has been shown to be associated with higher bioavailability than oral administration due to reduced first pass metabolism in a single and multiple ascending dose trial comparing intravaginal and oral administration (Trial 000076). Following single administration of quinagolide vaginal ring at a target release rate of quinagolide 4.5 µg/day, 9 µg/day or 13.5 µg/day [a], T_{max} was reached at 36-48 hours for all three doses and plasma concentration slowly declined over time for up to 35 days (Trial 000155). Furthermore, no dose accumulation and no impact on ovarian function or menstrual cyclicity were observed following sequential administration of quinagolide vaginal rings for two menstrual cycles (Trial 000207).

[a] The three strengths of quinagolide vaginal ring investigated in phase 1 trials are expressed in the content of quinagolide hydrochloride instead of quinagolide. The exact quantities of drug substance are minimally adjusted for the present trial due to a minor change in ring manufacturing. Quinagolide vaginal rings in phase 1 trials contain a dose load of quinagolide hydrochloride 400 µg, 800 µg and 1200 µg corresponding to a target release rate of quinagolide hydrochloride 5 µg/day, 10 µg/day and 15 µg/day, respectively, which are equivalent to a target release rate of quinagolide 4.5 µg/day, 9 µg/day and 13.5 µg/day.

Vaginal ring administration of quinagolide avoids repeated rapid daily rises of quinagolide levels as seen with oral administration and thereby has improved tolerability of quinagolide based on safety evaluations in phase 1 trials. In addition, an extended-release formulation with replacement of the vaginal ring every menstrual cycle is more suitable for the long-term management of endometriosis than a daily formulation.

In summary, as a novel non-hormonal drug inhibiting angiogenesis, quinagolide has the potential to address the unmet medical need for long-term treatment of endometriosis. Since quinagolide vaginal rings were shown to have favorable pharmacokinetic (PK) profiles without any anti-ovulatory or other undesirable side effects in the phase 1 trials, it is now possible to investigate the effect of quinagolide on reduction of moderate and severe endometriosis-related pain in endometriosis patients. The present phase 2 trial therefore aims at assessing the efficacy, safety and dose-response of three doses of quinagolide vaginal rings compared to placebo in women with moderate and severe endometriosis-related pain. The outcome of the present trial will help identify the appropriate dose(s) to be used for future trials.

1.3 Benefit / Risk Aspects

Benefits

Subjects will be randomized in a 1:1:1:1 ratio to placebo or one of the three quinagolide doses for four menstrual cycles. This means that 75% of endometriosis patients in the trial will be initially randomized to an active treatment and may benefit from relief of their endometriosis-related pain if the treatment is effective. All subjects in the trial will be provided with rescue analgesics to manage their endometriosis-related pain in case of insufficient pain relief. All subjects included in the trial will also benefit from close and comprehensive monitoring of their conditions.

It should be noted that the treatment and trial-related procedures are provided to the participating subjects free of charge, as Ferring compensates the investigational sites for their expenses.

Risks

The risks associated with this clinical trial, including the risks of investigational medicinal product (IMP), clinical and laboratory procedures and concomitant medications, are explained to subjects as part of the counselling prior to starting treatment.

Risks – Investigational Medicinal Product

In the clinical development program for endometriosis, quinagolide has been investigated intravaginally in a total of 111 women in phase 1 trials, of whom 23 were administered tablets at daily doses up to 75 µg and 88 were administered vaginal rings at a target release rate of up to 13.5 µg/day. In all trials, intravaginal administration of quinagolide was generally safe and well tolerated. The most common treatment-related adverse events with quinagolide vaginal rings (i.e. at a frequency of ≥5%, reported by more than 4 subjects) in phase 1 trials were headache, vaginal

discharge, nausea and dizziness. A more detailed description of the safety data from the individual trials is provided in the paragraphs below.

A lower frequency of gastrointestinal adverse events, i.e. nausea and vomiting, was reported following intravaginal administration of quinagolide 75 µg tablets once daily for 5 days, compared with oral administration (Trial 000076). The most frequently reported adverse events (i.e. reported by more than 1 subject) following intravaginal administration of quinagolide tablets were headache, dizziness and vaginal discharge. Single administration of quinagolide vaginal ring at a target release rate of quinagolide 4.5 µg/day, 9 µg/day and 13.5 µg/day was locally and systemically well tolerated with the most frequently reported adverse events being headache, vaginal discharge and nausea (Trial 000155). The majority of adverse events occurring in all treatment groups including the placebo group started during the first week of treatment and were considered to be of mild or moderate intensity. No inhibition of ovulation or modification of the menstrual cycle was observed during sequential administration of quinagolide vaginal ring at a target release rate of up to 13.5 µg/day (Trial 000207). In addition, quinagolide had no clinically significant effects on clinical chemistry, hematology or urinalysis parameters, nor on vital signs, electrocardiography (ECG) recordings, physical or gynecological examinations in any of the phase 1 trials.

Insertion and/or removal of the vaginal rings may be associated with mild discomfort or spotting, which is expected to be transient. Ring discoloration or breakage at glued junction points could also occur but based on the phase 1 data, there has been no safety concerns associated with these findings. New rings manufactured in a different way (i.e. injection-molded rings instead of glued rings) will be used in the present trial.

Quinagolide is currently marketed outside the United States as an oral tablet formulation for the treatment of hyperprolactinemia. The estimated cumulative exposure of quinagolide until now is more than 280,000 patient years, when administered as an oral tablet in the approved dose range of 25-300 µg or higher. The general safety profile of quinagolide is consistent with the class effects of other dopamine agonists, characterized by adverse events involving the gastrointestinal tract and central nervous system. The most frequent adverse drug reactions (all reported as very common, i.e. at a frequency of ≥10%) in relation to oral administration of quinagolide tablets are nausea, vomiting, headache, dizziness and fatigue. They occur predominantly during the first few days of the initial treatment or, as a mostly transient event, following dosage increase.

A serious but very rare risk associated with quinagolide oral tablets is syncope (<0.01%), which can be resulted from orthostatic hypotension. Orthostatic hypotension occurs at a frequency of 1-10% among patients treated with quinagolide oral tablets. Somnolence rarely (i.e. at a frequency of 0.01% to 0.1%) occurs during treatment with quinagolide oral tablets. Dopamine agonists other than quinagolide have been associated with sudden sleep onset episodes, particularly in patients with Parkinson's disease, and this has resulted in a general warning for the entire class of drugs. In rare cases (i.e. at a frequency of 0.01% to 0.1%), treatment with dopamine agonists has been associated with the occurrence of acute psychosis, which is reversible upon discontinuation.[20] Impulse control disorders involving pathological gambling, increased libido, hypersexuality,

compulsive spending or buying, binge eating and compulsive eating were rarely reported in association with the use of dopamine receptor agonists including quinagolide for the treatment of Parkinson's disease.[21] Ergot-derived dopamine agonists have been associated with an increased risk of fibrosis of the heart valves possibly through activation of 5-hydroxytryptamin 2B receptor (5-HT2B). Quinagolide is a non-ergot-derived dopamine agonist and does not have any 5-HT-receptor activity at clinically relevant doses.[22,23] Furthermore, no cases of valvular heart disease have been reported with quinagolide.

Quinagolide is not an embryotoxic or teratogenic agent. No adverse effects on embryos or fetuses were observed in the reproductive toxicity studies in rats and rabbits.[11] Based on clinical data for the treatment of hyperprolactinemia, pregnancy outcome data are available for 145 pregnancies in women exposed to quinagolide, with 106 pregnancies leading to live births. Among the 110 live-born neonates, a total of 5 malformations (4.5%) were reported, which is comparable to the 5-6% malformation rate reported among registered births.[24] In terms of pregnancy loss, 24 (16.6%) spontaneous abortions[b] were reported following exposure to quinagolide, which is similar to the 15-16% spontaneous abortion rate reported in the general population.[25] In addition, quinagolide has been investigated for the prevention of ovarian hyperstimulation syndrome (OHSS) in an in vitro fertilization study, in which 85 live births were reported following treatment with oral quinagolide tablets up to 200 µg/day for approximately 20 days without dose titration.[26] Quinagolide did not appear to show any detrimental effects on implantation, pregnancy or live birth rates.[26] In conclusion, exposure to quinagolide during early pregnancy has not been shown to increase the risk of pregnancy losses or congenital malformations compared with a normal pregnant population. Contraception counselling will be offered throughout the trial and condoms will be provided to all subjects at each clinic visit to avoid occurrence of pregnancy during participation of the trial. As a precautionary measure, a urine pregnancy test will be performed at least once per menstrual cycle in the present trial. If the test result is positive and confirmed by a serum βhCG test, the subject will be discontinued from the trial immediately and will be followed up until delivery (see section 8.4).

For further information regarding quinagolide, please refer to the Investigator's Brochure.[11]

Risks – Trial Procedures and Concomitant Medications

The primary endpoint and secondary efficacy endpoints in this trial are patient-reported outcome (PRO) measures that require the subjects' daily assessments of pain intensity, vaginal bleeding pattern, occurrence of sexual intercourse, analgesic use as well as daily and weekly assessments of pain impact, all of which impose no risks to subjects participating in the trial.

A few procedures will be performed at the investigational sites in this trial, i.e. transvaginal ultrasound, blood sampling, ECG, echocardiography, urine pregnancy test and urinalysis, which are either minimally invasive or non-invasive to subjects. The transvaginal ultrasound examinations may be associated with mild discomfort and a very rare risk of infection. The blood sampling might be associated with mild discomfort, bruising and a very rare risk of infection. ECG and

[b] Other pregnancy losses included 14 induced abortions (with 1 due to malformation) and 1 ectopic pregnancy.

echocardiography are harmless and painless tests associated with a very rare risk of mild rash where the electrodes are attached. Urine pregnancy tests and urinalysis, simply requiring subjects to urinate, impose no risks to subjects.

All subjects in this trial will be provided with rescue analgesics in the form of ibuprofen 200 mg, which is an approved medicinal product for pain relief and considered generally well-tolerated. The most frequently reported adverse effects with ibuprofen are gastrointestinal in nature and include nausea, vomiting, flatulence and diarrhea. Additional adverse effects may occur at high doses and under long-term treatment.[27] Clinical studies suggest use of ibuprofen, particularly at high doses (2400 mg/day), may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke).[27] Upper gastrointestinal ulcers, gross bleeding or perforation can occur in approximately 1% of patients treated with ibuprofen for 3-6 months.[27]

If needed, a strong analgesic hydrocodone-acetaminophen may be prescribed by the investigator. The most frequently reported adverse reactions with hydrocodone-acetaminophen are light-headedness, dizziness, sedation, nausea and vomiting.[28] Additional adverse effects may occur at overdose, under long-term treatment and during concomitant intake of alcohol or other drugs. The use of hydrocodone-acetaminophen may also cause mental or physical dependence, opioid addiction, abuse and misuse, which can lead to overdose and death. Serious, life-threatening or fatal respiratory depression may occur with use of hydrocodone-acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 mg per day, and often involve more than one acetaminophen-containing product.[28]

The investigator must assess each subject’s risks prior to prescription of hydrocodone-acetaminophen.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary Objective

- To evaluate the efficacy of three doses of quinagolide administered as an extended-release vaginal ring compared to placebo on reduction of moderate to severe endometriosis-related pain

Secondary Objectives

- To evaluate the effect of quinagolide vaginal ring on reduction of endometriosis-related dysmenorrhea, non-menstrual pelvic pain, dyspareunia and analgesic use
- To evaluate the effect of quinagolide vaginal ring on the subject's ability to function
- To evaluate the effect of quinagolide vaginal ring on ovarian function
- To evaluate the effect of quinagolide vaginal ring on endocrine parameters
- To evaluate the effect of quinagolide vaginal ring on vaginal bleeding pattern
- To evaluate the systemic exposure of quinagolide and metabolites after quinagolide vaginal ring administration
- To evaluate the effect of quinagolide vaginal ring on bone turnover markers
- To evaluate the safety profile of quinagolide vaginal ring including adverse events, symptoms of impulse control disorders, ECG and echocardiography findings, routine safety laboratory parameters and ring acceptability
- To validate the newly developed patient reported outcome (PRO) tool: Women's Endometriosis Diary [Note: this objective will be reported separately]

Exploratory Objective

- To explore the effect of quinagolide vaginal ring on endometriosis biomarkers such as angiogenic and inflammatory biomarkers

2.2 Endpoints

Primary Endpoint

- Changes in the mean daily Numerical Rating Scale (NRS) scores for the worst endometriosis-related pain at cycle 4

Secondary Endpoints

- Changes in the mean daily NRS scores for the worst endometriosis-related pain on days with menstrual bleeding (i.e. dysmenorrhea) and for the worst endometriosis-related pain on days with no menstrual bleeding (i.e. non-menstrual pelvic pain) at cycle 4
- Changes in the mean daily NRS scores for the worst endometriosis-related pain over 4 menstrual cycles
- Changes in the mean daily NRS scores for the worst dysmenorrhea over 4 menstrual cycles
- Changes in the mean daily NRS scores for the worst non-menstrual pelvic pain over 4 menstrual cycles

- Changes in the mean daily NRS scores for the worst dyspareunia on days with sexual intercourse over 4 menstrual cycles
- Frequency of avoiding sexual intercourse due to expected pain over 4 menstrual cycles
- Changes in the mean daily NRS scores for the worst impact of endometriosis-related pain on the subject's ability to function over 4 menstrual cycles
- Changes in the mean weekly scores of the Endometriosis Health Profile-30 (EHP-30) pain impact domain over 4 menstrual cycles
- Changes in vaginal bleeding pattern over 4 menstrual cycles
- Percentage of days with mild and/or strong rescue analgesics used over 4 menstrual cycles
- Total and average doses of mild and/or strong rescue analgesics used over 4 menstrual cycles
- Responder rate assessed as ≥30%, ≥50% and ≥70% reduction from the baseline in mean daily NRS score for the worst endometriosis-related pain, dysmenorrhea and non-menstrual pelvic pain and for the worst endometriosis-related pain impact, over 4 menstrual cycles
- Changes in the mean individual and total symptom and sign severity scores of the Biberoglu and Behrman (B&B) scale at cycle 4
- Changes in the EHP-30 scores over 4 menstrual cycles
- Changes in Patient Global Impression of Severity (PGIS) scores at cycle 4
- Patient Global Impression of Change (PGIC) scores at cycle 4
- Plasma concentration of quinagolide and metabolites during cycles 1 and 4
- Serum levels of mid-luteal phase progesterone at cycle 4
- Proportion of subjects with serum levels of mid-luteal progesterone ≥25 nmol/L (7.9 ng/mL) at cycle 4
- Serum levels of mid-luteal estradiol, prolactin, thyroid-stimulating hormone (TSH) and insulin-like growth factor-1 (IGF-1) at cycle 4
- Changes in bone turnover markers, determined by bone resorption marker serum C-terminal cross-linking telopeptide of type 1 collagen (s-CTx) and bone formation marker serum procollagen type I N propeptide (s-PINP) at cycle 4
- Changes in ECG parameters including PR interval, QT interval, corrected QT using Fridericia's formula (QTcF) and QRS interval at cycle 4
- Proportion of subjects with abnormal clinically significant echocardiography findings indicating valvular heart disease at cycle 4
- Proportion of subjects identified with potential impulse control disorders by the questionnaire for impulsive-compulsive disorders at cycle 4
- Frequency and intensity of adverse events
- Changes in circulating levels of clinical chemistry and hematology parameters, urinalysis parameters, and proportion of subjects with markedly abnormal changes
- Frequency and intensity of ring acceptability parameters over 4 menstrual cycles

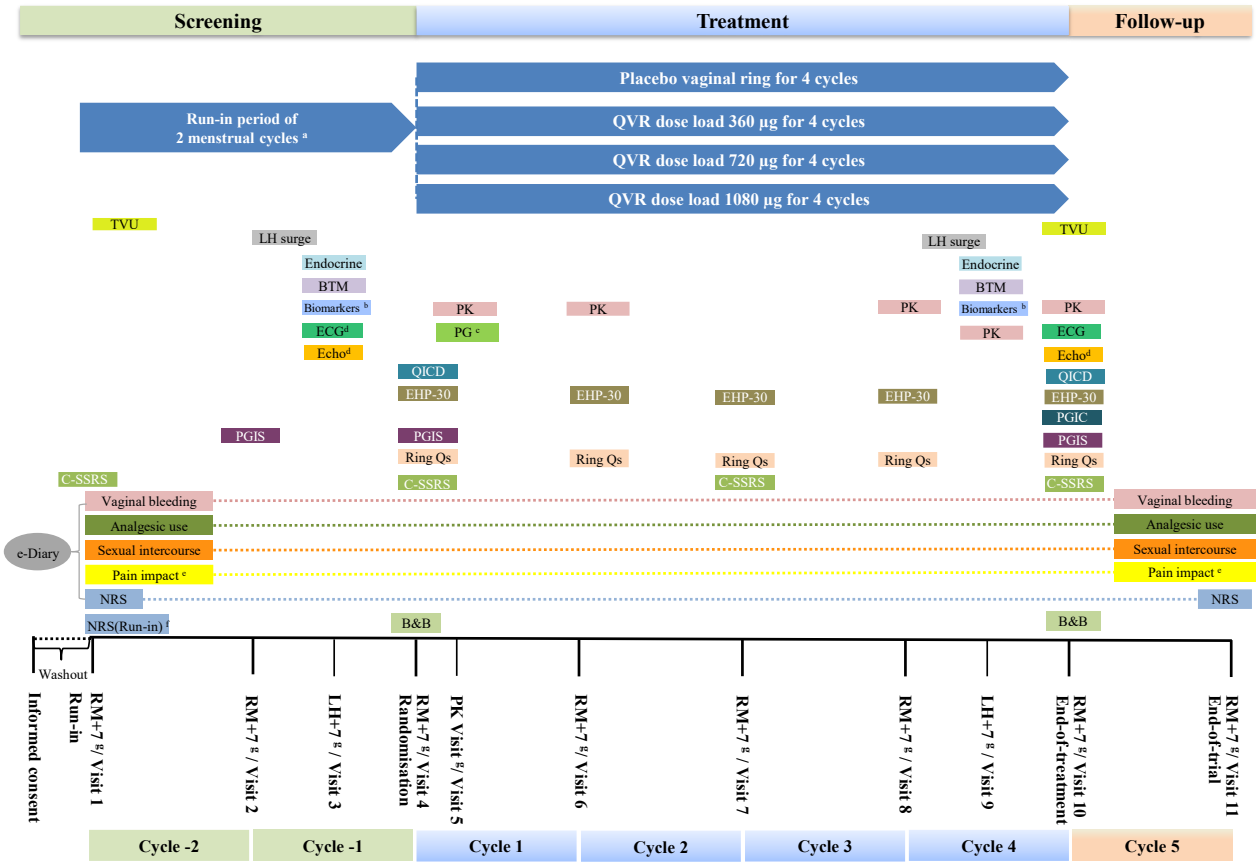
Exploratory Endpoint

- Changes in endometriosis biomarkers such as serum levels of VEGF, placenta growth factor (PlGF), interleukin 6 (IL-6) and soluble fms-like tyrosine kinase 1 (sFlt-1) at cycle 4

3 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

3.1.1 Trial Design Diagram



Abbreviations: B&B=Biberoglu and Behrman Scale, BTM=bone turnover markers, C-SSRS=Columbia Suicide Severity Rating Scale, Echo=echocardiography, ECG=electrocardiography, EHP-30=Endometriosis Health Profile-30 Questionnaire, LH=luteinizing hormone, LH+7=7 days after LH surge, NRS=Numerical Rating Scale, PGIC=Patient Global Impression of Change, PGIS=Patient Global Impression of Severity, PG=pharmacogenetic(s), PK=pharmacokinetic(s), QICD=questionnaire for impulsive-compulsive disorders, QVR=quinagolide vaginal ring, Ring Qs=ring acceptability questions, RM=return of menses, RM+7=day 7 of return of menses, TVU=transvaginal ultrasound

a In case of technical issues at the start of the run-in period, subjects are allowed to re-start cycle -2. Subjects that screen fail due to the temporary trial hold during the coronavirus disease 2019 (COVID-19) pandemic may be re-screened.
b Blood samples for potential endometriosis biomarkers will be collected for all subjects. If subjects provide a separate informed consent, additional blood samples for potential analyses of circulating cell-free DNA and microRNA will also be collected.
c If subjects provide a separate informed consent, a blood sample for pharmacogenetic analysis will be collected.
d ECG and Echo at screening can be arranged anytime during cycle -1 (e.g. at visit 3) but results must be available before randomization. ECG and Echo at cycle 4 can be performed within ±2 weeks of visit 10.
e Pain impact will be assessed on both a daily and a weekly basis.
f Scoring of the worst endometriosis-related pain during the past menstrual cycle on the NRS will be performed on paper at the run-in visit. Daily scoring of endometriosis-related pain on the NRS is captured by e-Diary.
g Visits on RM+7 or LH+7 can be scheduled RM+6-10 or LH+6-9, i.e. day 6 to day 10 of return of menses or 6-9 days after LH surge, respectively. PK visit (visit 5) can be arranged within 1-5 days of randomization (visit 4).

Figure 3-1 Trial Diagram – Trial Period

3.1.2 Overall Design and Control Methods

This is a randomized, double-blind, placebo-controlled, phase 2 trial assessing the efficacy, safety and dose-response of quinagolide extended-release vaginal rings administered sequentially for 4 menstrual cycles in women with moderate to severe endometriosis-related pain. In this trial, a menstrual cycle is considered the period from day 7 of return of menses (RM+7) in a cycle until the following day 7 of return of menses in the next cycle. Visits on RM+7 can be scheduled on RM+6-10, i.e. day 6 to day 10 of return of menses.

The trial consists of the following periods:

1) Screening: starting immediately after the signing of the informed consent(s) and including a run-in period of two complete menstrual cycles (cycles -2 and -1)
2) Treatment: double-blind, placebo-controlled treatment with three doses of quinagolide extended-release vaginal ring administered sequentially for four menstrual cycles (cycles 1, 2, 3 and 4)
3) Follow-up: post-treatment follow-up period of one menstrual cycle (cycle 5)

Screening: The screening period includes a wash-out period of approximately one month (only applicable to subjects currently using some hormonal products such as contraceptives [c]) and a run-in period of two complete menstrual cycles (cycles -2 and -1, applicable to all subjects). Subjects who are currently using some hormonal products such as contraceptives [c] may be eligible for the trial if they have completed the wash-out period. In this case, subjects need to sign the informed consent(s) before they discontinue those products. Discontinuation of the products should follow the labelling (e.g. completing the current cycle of contraceptives before wash-out). Subjects requiring wash-out will not be provided with the electronic diary (e-Diary) or rescue analgesics until the completion of the wash-out period, i.e. at the run-in visit.

Before entry into run-in, all subjects will be asked to score the worst endometriosis-related pain from a recall of their experience during the past menstrual cycle on a self-administered 11-point Numerical Rating Scale (NRS) with 0 indicating “no pain” and 10 indicating “worst imaginable pain”. After standardized training of e-Diary use, eligible subjects will be instructed to record endometriosis-related pain, vaginal bleeding, occurrence of sexual intercourse and analgesic use in the e-Diary on a daily basis. Impact of endometriosis-related pain on functioning will be assessed by subjects on both a daily and a weekly basis.

In this trial, endometriosis-related pain is evaluated as the pain located in the abdominal-pelvic area and the lower back area. During the run-in period, subjects will score the worst endometriosis-related pain during the preceding 24 hours on the NRS before bedtime every night in the e-Diary.

[c] Hormonal products requiring 1 month wash-out include GnRH antagonists, aromatase inhibitors, danazol and hormonal contraceptives (including combined oral contraceptive pill, progestin-only pill, transdermal patch and contraceptive ring). See section 4.3.1.

Vaginal bleeding will be recorded as "yes" or "no" on a daily basis in the e-Diary. If there is vaginal bleeding, subjects will be asked to register their bleeding volume (spotting, light, moderate or heavy bleeding) and to answer whether they think the bleeding is related to menses or not. Based on the subject's impression of whether she has menstrual bleeding or not, the NRS score obtained for the endometriosis-related pain is assigned to dysmenorrhea (endometriosis-related pain on days with menstrual bleeding) or to non-menstrual pelvic pain (endometriosis-related pain on days with no menstrual bleeding).

Occurrence of sexual intercourse ("yes" or "no") will also be recorded in the e-Diary. In case of sexual intercourse, subjects will be asked to score the worst pain experienced during or after intercourse (dyspareunia) on the NRS. In case of no sexual intercourse, subjects will be asked if it is due to expected pain.

Rescue analgesics for endometriosis-related pain will be limited to ibuprofen and/or hydrocodone-acetaminophen in this trial. As a mild analgesic, ibuprofen will be provided to subjects in the form of 200 mg oral tablets for their use on an as-needed basis. Subjects will be instructed not to use other analgesics unless necessary. If there is a need to change analgesics, subjects should discuss with investigators, who may prescribe a strong analgesic, i.e. 5 mg hydrocodone plus 300 mg or 325 mg acetaminophen (section 7.2.1.5). Use of any other analgesics for endometriosis-related pain is prohibited. Any prophylactic use of analgesics is also prohibited in this trial. Use of analgesics for endometriosis-related pain will be reported by subjects in the e-Diary on a daily basis.

The impact of the endometriosis-related pain on different aspects of functioning will be assessed by subjects both on the NRS on a daily basis and by the modified EHP-30 pain impact domain (i.e. the first 11 items plus an additional work item) on a weekly basis.[d]

Treatment: Subjects will be randomized on RM+7 of cycle -1 (at visit 4) if they, during the run-in period have moderate to severe endometriosis-related pain, which is defined as having a mean daily NRS score of ≥4 for the worst endometriosis-related pain during each run-in menstrual cycle. Randomization will be performed in a 1:1:1:1 ratio to quinagolide vaginal ring dose load 360 µg at a target release rate of quinagolide 4.5 µg/day, quinagolide vaginal ring dose load 720 µg at a target release rate of quinagolide 9 µg/day, quinagolide vaginal ring dose load 1080 µg at a target release rate of quinagolide 13.5 µg/day or placebo vaginal ring for four menstrual cycles (cycles 1, 2, 3 and 4).

Follow-up: Subjects will be followed up for one menstrual cycle (cycle 5).

From randomization to follow-up (cycle 1 to cycle 5), subjects will continue to use an e-Diary to score the endometriosis-related pain, to register vaginal bleeding pattern, occurrence of sexual intercourse and the analgesic use as well as to assess the impact of the worst endometriosis-related pain on functioning, as they have done in the run-in period.

[d] The secondary endpoint of changes in the weekly impact scores is based on the original EHP-30 pain impact domain, i.e. the first 11 items. The additional work item is used only for validation.

During the treatment period, subjects will self-insert the assigned ring in the upper part of the vagina on RM+7 of cycle 1 to cycle 4 at the clinic by following standard instructions for use. Supervision by the site staff can be provided if needed. After insertion, the vaginal ring will be kept in the vagina continuously for one menstrual cycle until being replaced with the next ring on RM+7 of the next cycle when the subject visits the clinic. Acceptability of the ring will be assessed by subjects via a ring acceptability questionnaire at each RM+7 visit during the treatment period. Unless under other effective birth control permitted by protocol (section 4.3.2), subjects will be required to use a non-hormonal single-barrier contraception (i.e. condom) from wash-out (if applicable) or run-in to end-of-trial. Contraception counselling and condoms will be offered to subjects throughout the trial.

B&B will be administered electronically at randomization and at cycle 4 (at visits 4 and 10), with trained trial coordinators completing the first part based on subjects' verbal responses and investigators completing the second part based on findings of a pelvic examination. Subjects will complete the electronic version of the EHP-30 questionnaire at randomization, and at every cycle from cycle 1 to cycle 4 (at visits 4, 6, 7, 8 and 10). PGIS scale will be completed electronically by subjects at cycle -2, at randomization and at cycle 4 (at visits 2, 4 and 10), while PGIC scale will be completed electronically at cycle 4 (at visit 10).

Blood samples will be collected throughout the trial for the purpose of evaluating mid-luteal phase endocrine parameters, bone turnover markers, endometriosis biomarkers, quinagolide and metabolites, and routine safety laboratory parameters. In this trial, mid-luteal phase is defined as 6-9 days after luteinizing hormone (LH) surge (LH+6-9) as tested by subjects at home by means of commercially available urinary LH kits. LH+7 visits can be scheduled on LH+6-9, either based on an actual LH surge date as indicated by a positive LH surge test or based on an estimated LH surge date according to subjects' cycle length if subjects fail to detect the LH surge. The exact cycle day of the LH+7 visit will be derived based on the first menstrual bleeding date of the current cycle confirmed at the RM+7 visits. An endocrine panel including estradiol, progesterone, prolactin, TSH and IGF-1 will be assessed during the mid-luteal phase of cycles -1 and 4 (at visits 3 and 9). Evidence of ovulation will be evaluated by serum levels of mid-luteal progesterone. Fasting blood samples for the analysis of a bone formation marker (s-PINP) and a bone resorption marker (s-CTx) will be collected during cycles -1 and 4 (at visits 3 and 9). Blood samples for endometriosis biomarkers including, but not limited to, VEGF, PlGF, IL-6 and sFlt-1 will also be collected during cycles -1 and 4 (at visits 3 and 9). At the same time points, if subjects have provided a separate informed consent, additional blood samples for potential analyses of circulating cell-free DNA and microRNA will also be collected. Routine safety laboratory tests for clinical chemistry and hematology parameters will be performed during cycle -1, at end-of-treatment and end-of-trial (at visits 3, 10 and 11). Quinagolide and metabolites will be measured within 1-5 days of first ring insertion, at RM+7 visits of cycles 1, 3 and 4 as well as at LH+7 visit of cycle 4 (at visits 5, 6, 8, 9 and 10) to assess systemic exposure and allow for population PK modelling. Blood samples should be taken prior to ring removal at RM+7 visits. If subjects have provided a separate informed consent, a blood sample for pharmacogenetic analysis will also be collected at visit 5.

ECG and echocardiography will be performed at screening and at end-of-treatment to monitor cardiovascular safety. ECG and echocardiography at screening can be arranged anytime during cycle -1, e.g. at LH+7 visit (visit 3) but results must be available prior to randomization. ECG and echocardiography at cycle 4 can be performed within ±2 weeks of visit 10.

A modified questionnaire for impulsive-compulsive disorders (QICD) will be completed electronically by trained trial coordinators based on subjects' verbal response prior to randomization at cycles -1 and 4 (at visits 4 and 10).

A urine pregnancy test will be performed at each clinic visit (except for visit 5) throughout the trial. If the test result is positive and is confirmed by a following serum βhCG test, the subject should be discontinued from the trial. Urinalysis is performed before entry into run-in (before or at visit 1) and at cycle 4 (at visit 10).

All subjects will be asked which treatment they believe they have received at the end of treatment. A sub-group of 60 subjects including 5 non-completers from selected sites, if they have provided a separate informed consent, will be invited to participate in a patient interview at the end of treatment to help determine the meaningful treatment benefit from the patients' perspective and to assess the content validity of the questions related to daily functioning in the e-Diary.

3.1.3 Trial Schedule

Estimated first patient first visit (FPFV):	Q3 2018
Estimated last patient last visit (LPLV):	Q3 2022

3.2 Planned Number of Trial Sites and Subjects

It is planned to randomize 280 subjects from approximately 100 sites in North America. It is estimated that around 590 subjects will be screened to randomize 280 subjects (70 subjects per treatment group) to achieve 208 evaluable subjects at the end of treatment. The sample size will be re-estimated by an external statistician during an interim analysis and the number of randomized subjects may be adjusted up to 360 (see section 9.1).

3.3 Interim Analysis

An interim analysis with the option to stop the trial early due to futility will be performed by an external statistician, when approximately half of the planned evaluable subjects (104 subjects) have completed the treatment period of the trial for the assessment of the primary endpoint. The unblinded data will be presented by treatment group. The futility bound is set at a conditional power using current trend equal to 5%, i.e. the trial could potentially be stopped for futility if the probability of achieving a significant result in the highest remaining dose group is lower than 5% based on the observed data at the interim analysis. In case of high drop-out rate or discontinuations in the highest dose group, the analysis will be performed on the remaining dose(s).

The futility bound is chosen at 5% conditional power using current trend, as it gives a relatively high probability (71%) of stopping the trial if the treatment has no effect, and a relatively low probability (1.4%) of stopping a trial that would have been successful in the end if the true treatment effect difference is 1.0 units. If the conditional power using current trend is between 5% and 90%, the sample size will be re-estimated and may be adjusted.

No interim analysis intended to stop the trial early due to overwhelming efficacy is planned.

The interim analysis will be performed based on cleaned data and the recruitment shall continue at the time of interim analysis unless otherwise notified.

3.4 Clinical Monitoring Committee

An internal Clinical Monitoring Committee consisting of the responsible medical officer, statistician and clinical trial manager will be established. The Clinical Monitoring Committee will meet regularly to evaluate the trial data including data with respect to the pre-defined stopping criteria (section 3.6.7). Data will be presented in a blinded manner.

3.5 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) consisting of exclusively external members will be established for this trial. The DMC members include external clinical experts, an external statistician and an ad hoc external cardiologist. None of the DMC members will be involved in the conduct of the trial.

The DMC will have access to the unblinded interim data presented by treatment group and will recommend whether the trial should be stopped or not according to the pre-specified futility criteria in the interim analysis. The DMC will also recommend whether the sample size should be adjusted.

If the stopping criteria on treatment group or trial level are met, the DMC will be requested to access the unblinded safety data presented by treatment group. The DMC will recommend whether one dose, several doses or the trial should be discontinued.

In any case, the DMC will keep the data and analyses confidential from any persons involved in the conduct of the trial. Sponsor representative(s) will only be allowed to attend the open sessions of the DMC meetings with no access to unblinded data.

A trial-specific DMC charter will specify its members, responsibilities and its working procedures.

3.6 Discussion of Overall Trial Design and Choice of Control Groups

3.6.1 Trial Design

The primary objective of the trial is to evaluate the efficacy of three doses of quinagolide administered as an extended-release vaginal ring compared to placebo on reduction of moderate to severe endometriosis-related pain.

Strict criteria have been incorporated in the design of this dose-finding trial to properly assess the treatment effect of quinagolide vaginal ring compared with placebo vaginal ring. In general, treatment and timing of ring insertion/removal and mid-luteal phase assessments according to individual menstrual cycle length, outcome measures consistent with guidelines for pain scoring and with other clinical trials on endometriosis have to a great extent been incorporated in the design of this trial.

This is a randomized, double-blind trial with placebo as the comparator to adequately evaluate the efficacy and safety of quinagolide vaginal ring. A placebo group is justified for this trial as there is a need to account for the placebo effect on pain relief in order to measure the absolute efficacy of the active treatment. In this trial, ethical concerns of using placebo controls have been addressed by providing subjects with rescue analgesics for pain relief as needed. Furthermore, the provision of rescue analgesics can help prevent dropouts due to lack of efficacy.

A run-in period of at least two menstrual cycles prior to randomization will provide consistent and reliable baseline data on pain scores for selecting subjects who truly experience moderate and severe endometriosis-related pain. Although a placebo run-in period has been widely used in clinical trials with placebo response, it has been argued that the placebo run-in does not lower the placebo response, increase the drug-placebo difference or affect the drug response rate post-randomization.[29] This has been further demonstrated in a recent trial for endometriosis-related pain, where the placebo effect did not appear to be diminished by the inclusion of a 4-week placebo run-in period.[30]

The placebo-controlled treatment period in this trial lasts for four menstrual cycles, which approximately corresponds to the active treatment duration of 18-20 weeks in the proof-of-concept study, where significant reductions in endometriosis lesions were observed following oral administration of quinagolide up to 75 µg.[16]

As described in sections 3.3 and 3.5, an interim analysis with the option to stop the trial early due to futility is planned when approximately half of the planned evaluable subjects have completed the treatment period of the trial. Should the DMC recommend to stop the trial early due to futility, the subjects would not need to continue in a trial without any treatment benefit so that an appropriate benefit/risk ratio for subjects participating in the trial could be guaranteed.

A double-blind design will ensure blinding and thereby unbiased evaluations by both the investigator and the subject, particularly the latter, as the primary and secondary efficacy endpoints in this trial are based on the PRO measures. Similarly, Ferring staff will also remain blinded to the

individual subject treatment allocation during the conduct of the trial. Precautions and measures taken to ensure double-blinding of the trial are described in detail in section 3.6.3. A multi-center setting of the trial will guarantee that the required number of subjects can be recruited within a reasonable time and also support subsequent generalization of the results.

A non-hormonal single-barrier contraception method (i.e. condom) is required for subjects participating in the present trial. Condom is the only feasible contraception method in this trial, as other contraception methods including hormonal contraceptive agents and intrauterine devices can interfere with the assessment of endometriosis-related pain. Throughout the trial, contraception counselling and condoms will be offered to avoid occurrence of pregnancy during the trial. In addition, as a precautionary measure, a urine pregnancy test will be performed at least once per menstrual cycle in the present trial. If the test result is positive and confirmed by a serum βhCG test, the subject will be discontinued from the trial immediately. Quinagolide is not an embryotoxic or teratogenic agent. No adverse effects on embryos or fetuses were observed in the reproductive toxicity studies in rats and rabbits.[11] Based on the available clinical data, exposure to quinagolide during early pregnancy has not been shown to increase the risk of pregnancy losses or congenital malformations compared with a normal pregnant population (see section 1.3).

All subjects will be asked to continue the e-Diary recording during the follow-up period of one menstrual cycle. Data collected from the follow-up period will help evaluate the maintenance of the treatment effect.

3.6.2 Selection of Endpoints

The primary endpoint of the present trial is the change in the mean daily NRS score for the worst endometriosis-related pain compared to placebo at cycle 4. Endometriosis-related pain is assessed as pain located in the abdominal-pelvic area and in the lower back area, which is the pain most often complained by endometriosis patients. It is considered appropriate to use a single "endometriosis-related pain" endpoint as the primary endpoint in this first trial investigating the efficacy of quinagolide in endometriosis patients. The major concern for using a summed score instead of two separate scores with one each for dysmenorrhea and non-menstrual pelvic pain is that the treatment effect of some hormonal drugs is driven by amenorrhea or oligomenorrhea, which can make a summed score unrepresentative of the true extent of improvement.[31] However, quinagolide does not affect ovarian function and thereby does not appear to modify the vaginal bleeding pattern.[11] It is therefore reasonable to believe that the treatment effect of quinagolide will not be driven by amenorrhea or oligomenorrhea and can be adequately measured by a single score for "endometriosis-related pain" as the primary endpoint in the present trial.

Subjects will be instructed to score the endometriosis-related pain at its worst during the preceding 24 hours every day before bedtime. Since pain assessment relies on memory, a short recall period of 24 hours, a response based on the worst experience during the day and standardized timing of assessment every night is usually preferable and is in line with clinical experts' and Food and Drug Administration (FDA)'s recommendations.[32,33,34] By asking subjects about their worst

endometriosis-related pain at the end of every day, the scoring has accounted for the worst pain occurring before any potential use of analgesics and has ensured a consistent recall period of 24 hours. Self-reporting of pain is considered to be the gold standard of chronic pain assessment, because it reflects the inherently subjective nature of pain.[32] The validated 11-point NRS widely used in clinical trials on chronic pain including endometriosis-related pain is selected to quantify the pain intensity.[30,31,32]

Based on women's subjective impression of whether they have menstrual bleeding or not, the daily NRS score on the worst endometriosis-related pain will be labelled as "endometriosis-related pain on days with menstrual bleeding" (dysmenorrhea) or "endometriosis-related pain on days with no menstrual bleeding" (non-menstrual pelvic pain). Dysmenorrhea and non-menstrual pelvic pain will be evaluated separately as secondary endpoints together with dyspareunia, since these are the three most common symptoms of endometriosis.

In addition to endometriosis-related pain intensity, vaginal bleeding, occurrence of sexual intercourse and dyspareunia, the use of rescue analgesics will be captured in an e-Diary as an objective measure of the pain relief.

The impact of the endometriosis-related pain on different aspects of functioning will be self-assessed both on a daily basis and on a weekly basis.

The B&B scale[35] has been widely used in other endometriosis trials and is selected for a secondary endpoint in the present trial for validation of the newly developed endometriosis PRO (i.e. Women's Endometriosis Diary). Since endometriosis patients can also have a compromised quality of life, a validated quality of life scale, EHP-30, developed specifically for endometriosis patients[36] will be administered to assess any improvement in functioning associated with treatment. PGIS as a static measure of global improvement with treatment and PGIC as a dynamic measure of global improvement with treatment[37] will both be assessed in the present trial to help determine the clinically important difference from the patients' perspective and thereby establish an appropriate definition of responders for future trials.

Plasma concentration of quinagolide and the active metabolites (M1 and M2) will be assessed to allow estimation of population PK parameters and investigation of the exposure-response relationships for efficacy over a range of doses to help select the dose(s) to be used in future trials. In phase 1 trials, high levels of M1 and M2 were detected in some healthy women after intravaginal administration.[11] No safety concerns are associated with high levels of metabolites. To investigate a relationship between the gene profiles and presence of high levels of metabolites, DNA samples will be collected for polymorphism genotyping in the enzymes responsible for the elimination processes of quinagolide for those subjects who have provided a separate informed consent.

Serum progesterone levels will be assessed at mid-luteal phase of cycle 4, corresponding to the end of treatment, to evaluate the impact of quinagolide on ovarian function. Other endocrine parameters include estradiol, prolactin, TSH and IGF-1. Additionally, to document that quinagolide does not have hypoestrogenic side effects on bone metabolism, blood samples will also be collected for the

assessment of the bone formation marker s-PINP and the bone resorption marker s-CTx, which are the recommended bone turnover markers in clinical trials.[38]

Safety endpoints include ECG and echocardiography to assess the cardiovascular risk profile of quinagolide, with special attention to drug-induced valvular heart disease. In order to detect any pathologic behaviors potentially associated with impulse control disorders during the use of dopamine receptor agonists, a modified questionnaire for impulsive-compulsive disorders will be completed at baseline and at the end-of-treatment. Other safety endpoints cover adverse events, ring acceptability, routine safety laboratory parameters and urinalysis.

3.6.3 Blinding

The present trial is double-blind. The subject, the investigator and other trial staff at the site will be blinded to treatment allocation during the conduct of the trial. Blinding is achieved by randomizing subjects in a 1:1:1:1 ratio to a vaginal ring containing quinagolide dose load 360 µg, 720 µg and 1080 µg or placebo, all of which are identical in appearance, flexibility and softness.

Similarly, the Ferring clinical team (e.g. data manager, statistician, clinical trial manager, clinical project leader, medical writer, pharmacovigilance physician, pharmacovigilance manager and medical officer) will be blinded to treatment allocation until breaking of the blind. The blind will be broken when the trial database is declared clean and is released to the responsible statistician.

As described in section 3.5, an external DMC will have access to unblinded interim data presented by treatment group and, if needed, unblinded safety data of some subjects presented also by treatment group. In any case, the DMC will keep the data and analyses confidential from the Ferring clinical team.

Since the primary endpoint and the secondary efficacy endpoints in this trial are based on PRO measures, precaution must be taken to ensure the blinding of subjects to treatment allocation throughout the trial. To avoid potential speculation of treatment allocation by comparing current pain scores against previous scores, subjects are not given any access to historically reported data after having submitted their answers in the e-Diary. Investigators, trial site staff and Ferring clinical team will also be blinded to the results of some laboratory parameters potentially linked to quinagolide's mechanism of action. In addition, all subjects will be asked at the end of treatment which treatment (quinagolide or placebo) they believe they have received to evaluate the risk of inadvertent unblinding. These practices are in line with FDA PRO guidance.[33]

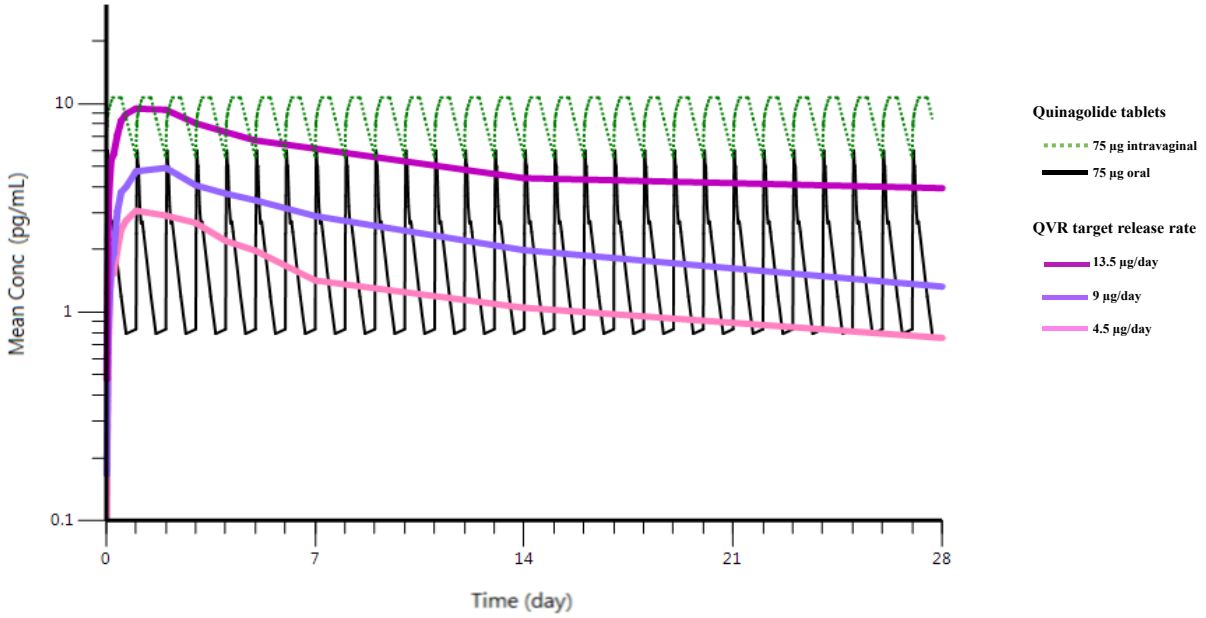
3.6.4 Selection of Doses in the Trial

In a dose-response trial it is desirable to test a relatively wide span of doses to identify the most appropriate dose(s) for future trials. The dose selection should also ensure that it is possible to discern clinically meaningful differences within a span that is acceptable with respect to subject safety.

Selection of doses in this trial is based on safety, tolerability and PK obtained from phase 1 trials. Oral administration of quinagolide at doses up to 75 µg once daily for 18-20 weeks appeared to reduce the size of lesions in endometriosis patients.[16] In the first phase 1 trial (000076), after repeated oral administration of 75 µg quinagolide tablets once daily for 5 days, the mean C_{max} was 8 pg/mL, the steady-state trough level was 0.8 pg/mL, and AUC_{tau} was 42.3 h*pg/mL. The corresponding values after intravaginal administration of 75 µg tablets was 13 pg/mL, 7 pg/mL and 225 h*pg/mL, respectively, which was 1.6-fold, 8-fold and 5-fold higher than after oral administration, demonstrating that intravaginal administration circumvents the first pass metabolism. It also showed that intravaginal administration had a slow absorption with approximately 8 hours to reach the maximum concentration compared with oral administration (T_{max} about 1 hour). Although intravaginal administration of quinagolide tablets up to 75 µg was associated with higher exposure, it was well tolerated with lower incidences of treatment-related adverse events, compared with oral administration.

In the subsequent trial (000155), quinagolide vaginal ring at a target release rate of quinagolide 4.5 µg/day, 9 µg/day and 13.5 µg/day were investigated. The plasma concentration of quinagolide increased initially in approximate proportionality. Following the initial peak, the plasma concentration declined slowly over the treatment period and the trough levels were maintained between 1-10 pg/mL for all three doses for up to 35 days. The median T_{max} following administration of quinagolide vaginal rings was approximately 36-48 hours for all three doses.

Selection of the doses in the present trial is based on the PK profiles obtained from these two phase 1 trials, which are illustrated in Figure 3-2 showing the mean observed PK parameters of the 75 µg oral and intravaginal tablets during a daily dosing interval extended to 28 days, compared to the PK profiles of quinagolide vaginal rings administered for 28 days. For the highest dose of quinagolide vaginal ring, the mean C_{max} of 10.9 pg/mL does not exceed the mean C_{max} of 13 pg/mL observed with the 75 µg intravaginal tablet. Following the initial peak, the concentration is similar to the mean C_{max} of 8 pg/mL observed with the 75 µg oral tablet. For the lowest dose of quinagolide vaginal ring, the mean concentration of quinagolide at day 28 resembles the steady state trough of 0.8 pg/mL observed with the 75 µg oral tablet. Therefore, for the three proposed doses of quinagolide vaginal ring, the maximum concentrations are below the maximum concentration of the 75 µg intravaginal tablet and the concentrations after the initial peak are within the concentration range of the 75 µg oral tablet.



Abbreviations: Conc=concentration, QVR=quinagolide vaginal ring

Figure 3-2 Dose Selection for Quinagolide Vaginal Ring

The proposed three doses provide a dose span with an equal absolute dose difference (i.e. a target release rate difference of 4.5 µg/day) to investigate the treatment effect of quinagolide. The outcome of the present trial should allow subsequent examination of the dose-response curve and to identify the dose(s) for quinagolide vaginal ring to be used in future trials.

The doses for the rescue analgesic medications used during this trial are in line with the recommendations in the respective product' labelling for the indication of pain relief.

3.6.5 Selection and Timing of Dose for Each Subject

In this clinical trial, the duration of treatment is based on individual subject's menstrual cycle length rather than calendar time points, matching the visits and timings of evaluation with the replacement of the vaginal ring. A menstrual cycle is considered the period between day 7 of return of menses (RM+7) in a cycle until the following day 7 of return of menses of the next cycle. Visits on RM+7 can be scheduled day 6 to day 10 day of return of menses (RM+6-10).

Subjects will be instructed to insert the assigned ring in the upper part of the vagina at RM+7 visits, a timing that corresponds to the stop of menstrual bleeding and is convenient for administration of a vaginal product, which can therefore easily be remembered and followed by subjects. The vaginal ring will be kept in the vagina continuously for one menstrual cycle until being replaced by the next

ring on RM+7 of the next cycle when the subject visits the clinic. Thus, quinagolide will be given sufficient time to inhibit the endometriotic lesions prior to return of the menses in the next cycle, when the majority of the most severe endometriosis-related pain occurs.

3.6.6 Selection of the Trial Population

The trial population consists of surgically confirmed endometriosis patients commonly included in clinical trials. After surgical treatment of endometriosis, these subjects still have recurrence of symptoms and moderate to severe endometriosis-related pain. Confirmation of endometriosis by laparoscopy or laparotomy is considered to be the gold standard for the diagnosis of the disease.[39] It is increasingly recognized that ultrasound evidence of endometrioma, combined with recurrent endometriosis-related pain, is a useful clinical diagnostic measure of endometriosis and can identify endometriosis with high accuracy.[40,41,42]

Moderate to severe endometriosis pain for this trial is defined as having a mean daily NRS score of ≥4 for the worst endometriosis-related pain during each run-in menstrual cycle. The cut-off of 4 is the most commonly recommended lower limit for moderate pain on NRS. Results of some other endometriosis studies were also taken into consideration in choosing this cut-off. In two recently completed pivotal phase 3 trials among 1689 endometriosis patients, a mean daily NRS score of approximately 5.5 was recorded for endometriosis pain at its worst during a baseline period of 35 days.[43] In an observational study for a minimum of 12 weeks, the 268 subjects reported a mean daily NRS score of 3.61 for endometriosis-related pain at its worst as well as a daily NRS score of ≥7 for at least 4 days.[44]

The trial will include pre-menopausal women ≥18 years without an upper age limit and will thereby cover the age span of most endometriosis patients.

The exclusion criteria incorporate the contraindications for the use of dopamine agonists and rescue analgesics.

3.6.7 Discontinuation Criteria (Stopping and Withdrawal Criteria)

The discontinuation criteria consist of criteria for discontinuation from treatment (stopping criteria) and criteria for discontinuation from trial (withdrawal criteria). For any premature discontinuation, an end-of-treatment visit (section 6.4.6) should be scheduled as soon as possible (preferably within 7 days of the last ring removal) and the investigator will obtain all the required details and document the date and the main reason of premature discontinuation in the electronic case report form (e-CRF).

Stopping Criteria (Discontinuation from Treatment)

Stopping Criteria on Subject Level

Subjects will be discontinued from the treatment if any of the following stopping criteria are met:

- Any significant changes in valvular regurgitation or stenosis from baseline associated with clinical signs and symptoms
- Any clinically significant abnormal ECG finding defined as prolongation of QTcF ≥500 msec or change from baseline QTcF value of ≥60 msec confirmed by the central cardiac laboratory
- Treatment-related syncope (orthostatic collapse associated with an abrupt, transient, complete loss of consciousness and inability to maintain postural tone, with rapid and spontaneous recovery) incompatible with continuing treatment
- Treatment-related alteration in consciousness or mental status (such as confusion, amnesia, loss of alertness and disorientation) incompatible with continuing treatment
- Treatment-related pathological behaviors of impulse control disorders including pathological gambling, compulsive buying, binge eating, and hypersexuality (see section 7.2.2.10) incompatible with continuing treatment
- Treatment-related acute psychosis, e.g. hallucinations/delusion

Stopping Criteria on Trial Level

The DMC will consider the following SAEs for stopping or modifying the trial (i.e. discontinuing one dose, several doses or the trial):

- One subject discontinued due to a diagnosis of cardiac valvulopathy confirmed by an independent cardiologist (see section 7.2.2.9)
- More than three subjects discontinued due to treatment-related syncope (orthostatic collapse associated with an abrupt, transient, complete loss of consciousness and inability to maintain postural tone, with rapid and spontaneous recovery)
- More than three subjects discontinued due to treatment-related significant alteration in consciousness or mental status (such as confusion, amnesia, loss of alertness and disorientation)

The DMC will be requested to access the unblinded safety data presented by treatment group and will recommend whether one dose, several doses or the trial should be discontinued based on the results of the analysis.

Withdrawal Criteria (Discontinuation from Trial)

Withdrawal from Trial

The subjects have the right to withdraw from the trial at any time for any reason, without the need to justify their decision. However, the investigator should record the reason for the subject's withdrawal, if possible. The investigator also has the right to withdraw subjects at his/her discretion.

The subject will be withdrawn from the trial if she experiences any of the following:

- Requiring a medical or surgical treatment that is prohibited by the protocol
- Becoming pregnant as confirmed by urine and serum βhCG pregnancy tests
- Becoming menopausal as confirmed by blood tests for endocrine parameters

Withdrawal may also occur, if the subject is non-compliant with the protocol procedures in a manner that could have major impact on efficacy or safety assessments.

Withdrawal of Consent

If the subject withdraws her consent, no further data will be obtained. However, already obtained samples may be analyzed. This will be described in the Informed Consent Documents. The subject can request destruction of samples, which would otherwise have been kept in storage.

3.6.8 Follow-up Procedures

No specific follow-up procedures are defined after the end-of-trial, except for safety follow-up procedures for subjects becoming pregnant during treatment (see section 8.4) and for subjects with unresolved adverse events classified as serious or considered to have a reasonable possible causality to the IMP (see section 8.6).

Access to Therapy after End-of-Trial

Concerning access to therapy after completion of the trial, quinagolide vaginal ring is currently under clinical development and cannot be offered to subjects after participation in this trial.

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

4.1.1 Inclusion Criteria

1. Informed consent(s) signed and dated prior to screening evaluations.
2. Pre-menopausal females aged ≥18 years at time of signing informed consent(s).
3. Body mass index (BMI) of 18-42 kg/m^2 (both inclusive) at screening.
4. Documentation of diagnosis by surgical visualization of endometriosis (laparoscopy or laparotomy) within the last 10 years before the run-in visit or visualization of persistent endometrioma (≥2 cm in diameter) by repeat ultrasound in two separate menstrual cycles before subject's entry into run-in.
5. Willing and able to use a non-hormonal single-barrier contraception (i.e. condom) from wash-out (if applicable) or run-in to the end-of-trial. This is not required if adequate contraception is achieved by vasectomy of the male sexual partner, surgical sterilization (e.g. tubal ligation and blockage methods such as ESSURE) of the subject or true abstinence of the subject (sporadic sexual intercourse with men still requires condom use).
6. Willing to avoid the use of vaginal douches or any other intravaginally administered medications or devices from randomization to the end of treatment.
7. Willing to change usual analgesics to rescue analgesics as permitted by protocol (protocol prohibited analgesics in section 4.3.1) for endometriosis-related pain from the start of run-in to the end-of-trial.
8. Willing to avoid any prophylactic use of analgesics from the start of run-in to the end-of-trial.
9. Willing to avoid any change in the use of non-drug therapy (e.g. acupuncture and physiotherapy) for endometriosis-related pain from the start of run-in to the end-of-trial.
10. Transvaginal ultrasound documenting a uterus with no clinically significant abnormalities (e.g. hysterectomy) and presence of at least one ovary with no clinically significant abnormalities with the exception of endometrioma (e.g. no evidence of ovarian cyst ≥5 cm, fibroid ≥4 cm, or presence of a submucosal fibroid) at the run-in visit.
11. Two regular menstrual cycles of 24-35 days (both inclusive) observed during the run-in period.
12. Having moderate to severe endometriosis-related pain defined as:
    - 12a) At the run-in visit, on a self-administered 11-point NRS, having an NRS score of ≥5 for the worst endometriosis-related pain during the past menstrual cycle.
    - 12b) At randomization, on the self-administered 11-point NRS, having a mean daily NRS score of ≥4 for the worst endometriosis-related pain during each run-in cycle.
13. Completion of the daily e-Diary for at least 80% of the days on average in two run-in cycles, from the day the e-Diary is available at the start of cycle -2 through the day before visit 4 at the end of cycle -1.

14. Documentation of a normal cervical cytology or negative results of human papilloma virus (HPV) reflex testing within 24 months of the start of run-in. If atypical squamous cells of undetermined significance were present on prior tests, additional follow-up HPV test results should be negative for high-risk viral subtypes.
15. Negative cervical swab for gonorrhea and chlamydia at screening.
16. Willing and able to comply with trial procedures, including filling in the e-Diary in English or Spanish, attending scheduled visits and adherence to treatment plan.

4.1.2 Exclusion Criteria

1. Use of depot medroxyprogesterone acetate (MPA) within 10 months of the start of run-in.
2. Use of GnRH agonists (3-month depot injection) or dopamine agonists within 6 months of the start of run-in.
3. Use of GnRH agonists (1-month depot injection or nasal spray) or birth control implants (e.g. NEXPLANON) within 3 months of the start of run-in.
4. Use of GnRH antagonists, aromatase inhibitors, danazol, intrauterine devices or hormonal contraceptives (including combined oral contraceptive pill, progestin-only pill, transdermal patch and contraceptive ring) within 1 month of the start of run-in.
5. Undiagnosed abnormal vaginal bleeding.
6. Current vestibulodynia and vulvodynia.
7. Chronic abdominal, pelvic or lower back pain diagnosed to be of non-endometriosis origin (e.g. presumptive adenomyosis as a dominant condition diagnosed by magnetic resonance imaging (MRI) or ultrasound, inflammatory bowel disease, interstitial cystitis, spinal disc herniation) that would interfere with the assessment of endometriosis-related pain.
8. Current diagnosis of a chronic pain syndrome (e.g. fibromyalgia, chronic back pain, myofascial pain syndrome, chronic headache) or any other condition that requires continuous use of analgesic therapy.
9. Known bone diseases (e.g. osteoporosis, Paget's disease and osteomalacia) affecting bone resorption or bone formation markers.
10. Chronic endocrine abnormality affecting the hypothalamic-pituitary-gonadal axis or leading to ovarian dysfunction except for hyperprolactinemia.
11. Known positive results of hepatitis B virus, hepatitis C virus and human immunodeficiency virus (HIV) antibody tests.
12. History of no relief of endometriosis-related pain after any medical therapy or surgery. However, history of partial pain relief, discontinuation due to side effects from medical therapy or non-adherence to post-surgery medical therapy are not exclusionary.
13. History of having used more than 2 consecutive weeks of a prohibited long-acting narcotic or immediate-release narcotic for treatment of endometriosis-related pain within 6 months of the start of run-in.
14. History of malignancy within 5 years of the start of screening, except for adequately managed basal cell carcinoma and squamous cell carcinoma of the skin.
15. History of recurrent bacterial / fungal vaginal infection or recurrent urinary tract infection (all defined as ≥4 episodes within a year).

16. History of orthostatic hypotension or recurrent syncope.
17. History of mental illness including occurrence of acute psychosis, bipolar disorders and schizophrenia (except for well-controlled anxiety and/or depression with no changes to interventions for 6 months prior to start of run-in).
18. History of impulse control disorders including pathological gambling, compulsive buying, hypersexuality, and binge eating or being identified with potential impulse control disorder by the questionnaire for impulsive-compulsive disorders (a score ≥2 for any sub-questions of Question 3 or a score ≥1 for any sub-questions of Question 4) prior to randomization.
19. History of valvular heart disease.
20. History of sudden sleep onset episodes.
21. Any clinically significant abnormal findings from vital signs, urinalysis, blood tests of hematology and clinical chemistry at screening, including a drop of 20 mmHg of systolic blood pressure or a drop of 10 mmHg of diastolic blood pressure within three minutes of standing from a sitting position, alanine aminotransferase (ALT) >2.5 times upper limit of normal (ULN) or bilirubin >1.5 times ULN or creatinine >1.5 mg/dL.
22. Any clinically significant abnormal findings from blood test of endocrine parameters (including signs indicating menopausal status but excluding hyperprolactinemia) at screening.
23. Any clinically significant abnormal findings from physical examination at screening.
24. Any vaginal or vulvar lesions that could interfere with vaginal ring usage.
25. Any significant abnormal ECG or echocardiography findings (e.g. valvular regurgitation or stenosis) before randomization.
26. Any recent suicidal ideation of type 4 (i.e. active suicidal ideation with some intent to act, without specific plan) or type 5 (i.e. active suicidal ideation with specific plan and intent), or any recent suicidal behavior identified by the electronic Columbia-Suicide Severity Rating Scale at screening.
27. Hypersensitivity to any active ingredient, excipients or other component of medicinal products used in the trial, including quinagolide vaginal ring, placebo vaginal ring and ibuprofen.
28. Known serious adverse drug reactions to dopamine agonist.
29. Current or history of gastrointestinal ulcer or gastrointestinal bleeding within 6 months of the run-in visit.
30. Current pregnancy as confirmed by a positive serum βhCG test at screening or planning a pregnancy within the duration of the trial, currently breast-feeding or less than 6 months post-partum of the run-in visit.
31. Planned surgical treatment of endometriosis or planned surgery in the abdominal-pelvic or lower back area within the duration of the trial that could interfere with the efficacy assessment.
32. History of drug abuse within 2 years of the start of screening or a current positive urine drug screen, unless the cause of the positive result is from opioids and antidepressants that are medically indicated and prescribed by a physician.
33. Current or history of alcohol abuse within 2 years of the start of the run-in visit.

34. Current or previous participation in a clinical trial involving a non-registered investigational medicinal product within 1 month of the run-in visit. If the trial involves a hormonal drug, the exclusion criteria 1-4 shall apply.

4.2 Method of Assigning Subjects to Treatment Groups

4.2.1 Recruitment

The participating subjects will be recruited from clinics included in the trial. Advertisements may be used if approved by relevant Institutional Review Boards (IRBs), as applicable to local regulations.

A screening number is allocated to each subject who has given informed consent to participate in the trial. A subject must always be assigned to the lowest available screening number at each site. A subject screening / enrolment log for all screened subjects must be maintained by the investigator.

4.2.2 Randomization

On RM+7 of menstrual cycle -1, eligible subjects will be randomized in a 1:1:1:1 ratio to quinagolide vaginal ring dose load 360 µg, quinagolide vaginal ring dose load 720 µg, quinagolide vaginal ring dose load 1080 µg or placebo vaginal ring for four menstrual cycles (cycles 1, 2, 3 and 4).

An independent statistician at the Ferring Global Biometrics Department will create a computer-generated randomization list and randomization is performed centrally through the e-CRF prior to the insertion of the first vaginal ring. Thereby each subject will receive a unique randomization number generated in the e-CRF system. The randomization is stratified by site, i.e. whole blocks are assigned to sites.

4.3 Restrictions

4.3.1 Prohibited Medications / Therapies

Prohibited Medications / Therapies before the Trial and during the Trial

The following concomitant medications and therapies are prohibited for the following period before the start of the run-in to the end-of-trial:

Prohibited medications / therapies	**Examples**	**Minimum prohibited period before run-in**
Depot MPA	DEPO-PROVERA	10 months
GnRH agonist (3-month depot injection)	LUPRON, ZOLADEX	6 months
Dopamine agonist	bromocriptine (PARLODEL) cabergoline (DOSTINEX)	6 months
GnRH agonist (1-month depot injection or nasal spray)	LUPRON, ZOLADEX, SYNAREL	3 months
Birth control implants	NEXPLANON	3 months
Intrauterine device (IUD)	MIRENA	1 month
GnRH antagonist		1 month
Aromatase inhibitor		1 month
Danazol	CYCLOMEN	1 month
Hormonal contraceptives*	combined oral contraceptive pill, progestin-only pill, transdermal patch and contraceptive ring (NuvaRing)	1 month

*Discontinuation of hormonal contraceptives should follow the labelling of the product (e.g. completing the current cycle of contraceptives before wash-out). Emergency contraceptives ELLA 30 mg and levonorgestrel 1.5 mg are allowed from randomization to the end-of-trial

Prohibited Medications / Therapies during the Trial

In addition to medications/therapies listed above, the following medications/ therapies are also prohibited from the start of the run-in to the end-of-trial:

Prohibited medications / therapies	**Examples**
COX2 inhibitors	CELEBREX
Immediate-release strong narcotic analgesics	Oxymorphone Hydromorphone Morphine (oral and IV) Fentanyl (sublingual, IV, injections)
Any extended-release (ER), controlled-release (CR) or long-acting narcotic analgesics	CR/ER morphine CR/ER hydromorphone CR/ER oxymorphone CR/ER oxycodone ER tapentadol ER tramadol Methadone Levorphanol Fentanyl (transdermal patch)
Medical marijuana	
Prescription amphetamine	
RITALIN	
Prohibited medications / therapies from randomization to the end-of treatment	
Vaginal douches or any other intravaginally administered medications or devices	

Prohibited Therapy after the Trial

It is also prohibited to continue therapy outside the scope of the trial with any medicinal products provided specifically for the trial.

4.3.2 Other Restrictions

Subjects will be required to fast overnight (no food or drinks except for water after midnight) before LH+7 visits of cycles -1 and 4 (visits 3 and 9) due to blood sampling for analysis of bone turnover markers.

Subjects must be willing and able to use an acceptable effective contraception method throughout the trial. The method used by subjects must be documented. In the context of this trial, acceptable contraception methods include:

- A non-hormonal single-barrier contraception (i.e. condom)
- Documented vasectomy of the male sexual partner
- Surgical sterilization (e.g. tubal ligation or blockage methods such as ESSURE) of the subject
- True abstinence of the subject (sporadic sexual intercourse with men still requires condom use)

4.4 Subject Replacement

A subject can only be assigned one screening number and one randomization number unless she is re-screened. Subjects re-screened due to the COVID-19 pandemic will receive new screening numbers. The screening and randomization number are unique and cannot be re-used. Subjects who are discontinued prematurely after randomization are not to be replaced.

5 TREATMENTS

5.1 Treatments Administered

5.1.1 Investigational Medicinal Products (IMPs)

The investigational medicinal products (IMPs) in the present trial will be supplied as vaginal rings containing quinagolide 360 µg, 720 µg, 1080 µg or its matching placebo. Quinagolide vaginal ring is a vaginal delivery system which allows for the extended release of quinagolide for up to 35 days. The three strengths of quinagolide vaginal rings investigated in the present trial have a target release rate of quinagolide 4.5 µg/day, 9 µg/day and 13.5 µg/day, respectively. Quinagolide or placebo vaginal ring is inserted on RM+6-10 of a cycle and is kept in the vagina continuously until being replaced by a new ring on RM+6-10 of the next cycle.

On RM+7 of cycle -1 (at visit 4), eligible subjects will be randomized in a 1:1:1:1 ratio to quinagolide vaginal ring dose load 360 µg, quinagolide vaginal ring dose load 720 µg, quinagolide vaginal ring dose load 1080 µg or placebo vaginal ring, administered once per menstrual cycle and sequentially for four menstrual cycles (cycles 1, 2, 3 and 4).

The vaginal ring will be inserted and removed by the subject herself at the RM+7 visits to clinic by following the standard instructions for use provided to each subject, irrespective of whether the subject is still experiencing menstrual bleeding. If needed, supervision by site staff can be provided and the lubricant allowed for this trial (i.e. KY Jelly) can be used. If the ring is expelled, it can be rinsed and re-inserted by the subject at home. In case the ring is expelled during the non-menstrual period but is impossible to re-insert, a visit to the clinic for ring replacement must be arranged as soon as possible and no later than 3 days after ring expulsion. If the ring is expelled during the menstrual period and is impossible to re-insert, it is up to the investigator to decide whether a replacement ring is needed or not. Subjects are recommended not to take out the ring for sexual intercourse. If a ring is out of the body for more than 24 hours, subjects should not re-insert the ring but contact the site for ring replacement.

5.1.2 Non-Investigational Medicinal Product (NIMP)

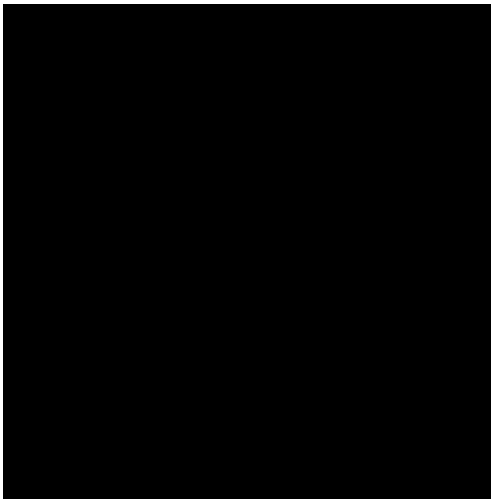
The non-investigational medicinal product (NIMP) in the present trial is 200 mg film-coated, capsule-shaped ibuprofen tablets with the trade name MOTRIN IB, which is provided by Ferring as mild rescue analgesics to subjects from start of run-in to the end-of-trial. Subjects are allowed to take ibuprofen for their pain relief on an as-needed basis but the maximum amount is 800 mg (4 tablets) per dose and 3200 mg (16 tablets) per day.[27] The specific dosing regimen will be decided by the investigator in accordance with the labelling of prescription ibuprofen doses.[27]

If required, a strong rescue analgesic hydrocodone-acetaminophen may be prescribed by the investigator but this will not be provided by Ferring and is not a NIMP. Details are specified in section 7.2.1.5.

5.2 Characteristics and Source of Supply

5.2.1 Investigational Medicinal Product

All IMPs are provided by Ferring and will be handled according to the principles of Good Manufacturing Practice (GMP). All sites will be provided with quinagolide and placebo vaginal rings in amounts sufficient for the trial. Quinagolide vaginal ring and placebo vaginal ring are indistinguishable with identical appearance. All vaginal rings are soft, flexible, off-white, translucent, toroid shaped rings with a major diameter of 54 mm and a minor diameter of 4.1 mm. The vaginal rings are latex-free.



5.2.2 Non-Investigational Medicinal Product

Ibuprofen is provided by Ferring as MOTRIN IB 200 mg film-coated, capsule-shaped tablets for oral administration and will be handled according to the principles of GMP.

5.3 Packaging and Labelling

Packaging and labelling of the IMPs and NIMP will be performed under the responsibility of the Clinical Trial Supply Department at Ferring Pharmaceuticals A/S in accordance with GMP, Annex 13, EudraLex Volume 4 and national regulatory requirements. Details on the packaging of each medicinal product are provided in Table 5-2.

Table 5-2 Packaging of Medicinal Products

IMP / NIMP	Packaging
IMP: Quinagolide / Placebo vaginal ring	Each vaginal ring is packaged in an individual foil moisture barrier pouch with re-closable gripper and tear notches.
NIMP: Ibuprofen	Ibuprofen is provided in commercial bottles of 50 or 100 film-coated, capsule-shaped tablets per bottle packed individually in commercial cartons.

The NIMP in the present trial is commercially available and will be purchased centrally. No modification to the usual commercial state of the product will be made, except for trial-specific labelling. Thus, quinagolide vaginal rings, placebo vaginal rings and ibuprofen will all be labelled with trial-specific labels in accordance with applicable requirements in the country(ies) where the trial is conducted.

5.4 Conditions for Storage and Use

The investigator will ensure that the medicinal products will be stored in appropriate conditions in a secure location with controlled access. The storage compartment shall be monitored regularly and the temperature shall be documented in accordance with the instructions provided by the sponsor.

Deviations in storage temperature must be reported to the sponsor as instructed in the IMP/NIMP handling guideline.

Quinagolide and placebo vaginal rings must be stored frozen (-25°C to -10°C) (-13°F to 14°F). The rings will be taken out from the freezer at least 30 minutes but not more than 24 hours prior to insertion.

Ibuprofen must be stored at 20°C to 25°C (68°F to 77°F).

For information on warnings, precautions and treatment of overdose, please refer to the Investigator's Brochure for the IMP and to the approved labelling of the NIMP.[11,27]

5.5 Blinding / Unblinding

5.5.1 Blinding

Quinagolide and placebo vaginal rings, including replacement rings, will be packaged in accordance with a computer-generated randomization list prepared for all trial sites.

All packaged IMP kits will be indistinguishable with identical appearance and will be labelled with random identification numbers which are linked to the treatment allocation. Once the subject is assigned a unique randomization number in the e-CRF system, the subject's treatment allocation will be transferred automatically to the Interactive Response Technology (IRT) system. Site staff will access the IRT system to obtain an identification number for the vaginal ring to dispense to the subject, with both the site staff and the subject blinded to the treatment allocation. In case of ring replacement, the identification number for the replacement ring will also be obtained from the IRT system. All vaginal rings will be indistinguishable with identical appearance, flexibility and softness. Subjects, investigators and other site staff as well as in-field monitors will be blinded to treatment allocation throughout the trial.

The personnel at the central laboratory analyzing blood samples for quinagolide and metabolite concentration will be unblinded to treatment allocation, but the personnel at the other central laboratory analyzing blood samples will be blinded to treatment allocation throughout the trial. As described in section 3.5, an external DMC will have access to unblinded interim data presented by treatment group and, if needed, unblinded safety data of some subjects presented also by treatment group. In any case, the DMC will keep the data and analyses confidential from the Ferring clinical team. Ferring clinical team e.g. data manager, statistician, trial manager, clinical project leader, medical writer, pharmacovigilance physician, pharmacovigilance manager and medical officer will be blinded to treatment allocation until breaking of the blind. The blind will be broken when the trial database is declared clean and is released to the responsible statistician.

The randomization list will not be available to any person involved in the conduct and evaluation of the trial until the trial database is declared clean and is released to the responsible statistician, except for the release to the external statistician for the interim analysis. Likewise, the treatment allocation information will not be accessible to investigators, trial staff at the site or central laboratory personnel during the trial.

5.5.2 Unblinding of Individual Subject Treatment

An emergency unblinding procedure will be available to the investigator and designated persons at Ferring through the e-CRF. It is the investigator's responsibility to decide whether it is medically necessary to know the investigational product the subject receives (i.e. unblinding) to ensure the subject's welfare and safety, and thereby the responsibility to break the blind for individual subjects in emergency situations resides with the investigator. Breaking of the blind for individual subjects in emergency situations could be required in case of a suspected unexpected serious adverse

reaction (SUSAR) or in case of an important adverse event where the knowledge of the IMP in question is required for therapeutic decisions for the management of the subject.

The investigator/person who unblinds a subject's treatment will use the e-CRF in which he/she is required to enter a password and record the reason for unblinding before the treatment code can be broken. The e-CRF automatically records when and by whom the code is broken. The investigator must record the event of unblinding in the subject's medical record, including the reason for unblinding, but not the treatment allocation if this can be avoided. The investigator should notify the IRB about the circumstances for unblinding in accordance with local requirements.

In case of accidental unblinding, the same procedure as for emergency unblinding must be followed, i.e. the person who is accidentally unblinded will enter a password in the e-CRF and must record the reason for unblinding, while the e-CRF records when and by whom the code is broken.

If Ferring needs to unblind a subject's treatment, the e-CRF will be used for unblinding. It is required to enter a password and the reason for unblinding before the treatment code can be broken. The e-CRF records also when and by whom the code is broken. The code break will occur according to corporate standard operating procedures for unplanned unblinding of trial subjects. It may be necessary to unblind an individual subject's treatment for the purposes of expedited reporting to the relevant health authorities and/or IRBs. In that situation, every effort will be made to maintain blinding of sponsor personnel involved in data analysis and interpretation. Other personnel may be unblinded for SUSARs, including trial site staff as well as staff acting on behalf of Ferring.

Information on whether the blind has been broken for any subjects is available in the e-CRF and must be collected before the database is declared clean and is released to the responsible statistician.

In case the e-CRF cannot be accessed and hence the emergency unblinding cannot be performed within the e-CRF system, the investigator should contact Ferring Pharmacovigilance using the contact details given below.

Ferring Pharmacovigilance

[redacted]

If Ferring Pharmacovigilance cannot access the e-CRF, a back-up procedure involving the e-CRF vendor is in place.

5.6 Treatment Compliance

5.6.1 Dispensing and Accountability

The IMP must only be dispensed to and inserted by subjects who meet the eligibility criteria and are randomized to a treatment group in the trial. The site staff will use an IRT system to assign and dispense IMP and NIMP kits. The dates and quantities of IMP and NIMP dispensed to and returned

by each subject will also be recorded in the IRT system to manage the overall drug accountability for each subject. The in-field monitor will review and verify the drug accountability of the IMPs and NIMP throughout the trial. Any discrepancies will be documented.

5.6.2 Assessment of Compliance

Compliance with IMP treatment regimen is assessed by dates of vaginal ring insertion and ring removal for each cycle.

5.7 Return and Destruction of Medicinal Products

All used and unused IMPs and all unused NIMP will be returned to Ferring as instructed by the Ferring Clinical Trial Supply Department. All used IMPs should be stored frozen (-25°C to -10°C) (-13°F to 14°F) until being returned. A subset of the used vaginal rings, returned under temperature controlled shipment, will be analyzed for aspects such as residual quinagolide content and ring discoloration. Results of such analyses will be reported separately. The return shipment will be arranged after drug accountability has been verified by the in-field monitor and signed off by the investigator.

5.8 Auxiliary Supplies

Ferring will provide the trial sites with lubricants for ring insertion and/or removal. Any unused supply of lubricants will be returned or destructed upon trial site closure.

6 TRIAL PROCEDURES

Table 6-1 Trial Flow Chart – Procedures at Clinics

	Screening [a, b]						Treatment [b]										Follow-up [b]
	Wash -out[a]	Start of Run-in	Run-in period				Cycle 1			Cycle 2		Cycle 3		Cycle 4			Cycle 5
			Cycle -2		Cycle -1												
	~1 cycle before run-in	V1		V2	V3	V4	V5		V6		V7		V8	V9	V10		V11
		RM +7	LH +7	RM +7	LH +7	RM +7	1-5d of V4	LH +7	RM +7	LH +7	RM +7	LH +7	RM +7	LH +7	End-of-treatment[c] RM+7		End-of-trial[c] RM+7
Written informed consent(s)	X	X[d]															
NRS (last cycle) on paper		X[d]															
eC-SSRS		X[d]				X[e]					X[f]				X[f]		
Inclusion/exclusion criteria	X	X[d]		X	X	X[e]											
Demographics, history, BMI		X[d]															
Vital signs		X[d]				X[e]	X[g]								X[g]		
ECG					X[g,h]										X[g,h]		
Echocardiography (Echo)					X[h]										X[h]		
Physical exam		X[d]													X		
Gynecological (GYN) / pelvic exam [i]		X[d]				X[j]									X		
Cervical swab		X[d]															
Transvaginal ultrasound (TVU)		X[d]													X		
Urine pregnancy test [k]		X[d]		X	X	X[e]			X[j]		X[j]		X[j]	X	X[j]		X
Urine drug screen		X[d]				X[e]											
Urinalysis		X[d]													X		
Blood sample (safety lab)					X										X		X
Blood sample (endocrine)					X									X			
Blood sample (fasting BTM)					X									X			
Blood sample (biomarkers [l])					X									X			
Blood sample (PK)							X		X[j]				X[j]	X	X[j]		
Blood sample (PG [m])							X										
e-Diary review		X .....X[e].....															X
QICD						X[e]									X[f]		
Randomization						X											
EHP-30 questionnaire						X[j]			X[f]		X[f]		X[f]		X[f]		
PGIS scale				X		X[j]									X[f]		
PGIC scale															X[f]		
B&B scale						X[i,j]									X[f,i]		
Menstruation dates		X		X		X			X		X		X		X		X
Insertion/removal of ring						X			X		X		X		X		
Ring acceptability questionnaire						X			X		X		X		X		
Drug accountability				X	X	X			X		X		X	X	X		X
Concomitant medications	X	X		X	X	X	X		X		X		X	X	X		X
Adverse events	X	X		X	X	X	X		X		X		X	X	X		X
Dispense/prescribe rescue med.		X		X	X	X			X		X		X	X	X		
Dispense/remind contraception		X		X	X	X	X		X		X		X	X	X		
LH surge kit dispensing		X									X						
LH surge test reminders				X									X				
End-of-treatment question & form															X		

BTM=bone turnover markers, eC-SSRS=electronic Columbia-Suicide Severity Rating Scale, QICD=Questionnaire for Impulsive-Compulsive Disorders, V=visit

a The screening period includes a wash-out period of about 1 month (applicable to some subjects) and a run-in period of 2 cycles (applicable to all subjects)

b In this trial, a menstrual cycle is considered the period between day 7 of return of menses (RM+7) in a cycle until the following RM+7 Visits on RM+7 or LH+7 can be scheduled on RM+6-10 or LH+6-9, i e day 6 to day 10 of return of menses or 6-9 days after LH surge, respectively No visits needed for grayed LH+7 columns

c In case of premature discontinuation, an end-of-treatment visit should be arranged as soon as possible, preferably within 7 days of the last ring removal (section 6 1 1)

d Performed before entry into run-in (before or at visit 1 but not before wash-out visit) Subjects must receive a signed copy of ICF(s) before trial-related procedures

e Performed before randomization

f Performed prior to other non-PRO procedures at the visit This requirement also applies to B&B first part

g Performed before blood sampling, when applicable

h ECG and Echo at V3 can be done anytime during cycle -1 but results must be available before randomization ECG and Echo at V10 can be done ±2 weeks of V10

i GYN exam at V1 and V10; pelvic exam at V4 for B&B second part (section 7 4 12) B&B first and second parts completed by different staff (section 7 2 2 1)

j Performed after randomization but before ring insertion or removal

k If the urine pregnancy test result is positive, a serum βhCG test must be performed

l Samples for endometriosis biomarkers taken for all subjects Additional samples for cell-free DNA/microRNA if a separate consent is obtained (section 7 3 1)

m Pharmacogenetic (PG) testing is performed if subjects have provided a separate informed consent (section 7 4 22)

The flow of the self-assessments by the subjects in an e-Diary is shown in Table 6-2. The e-Diary should be completed by the subjects before bedtime every night throughout the trial.

Table 6-2 Trial Flow Chart – Self-assessments by Subjects

	Screening[a]				Treatment						Follow-up[a]
	V1[a]	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11[a]
Daily self-recording by subjects in e-Diary											
NRS	X.....X										
Ocurrence of sexual intercourse	X.....X										
Pain impact [b]	X.....X										
Vaginal bleeding	X.....X										
Analgesics use	X.....X										

NRS=Numerical Rating Scale, V=visit

a Subjects should complete the e-Diary before bedtime every night from run-in to follow-up, i.e. from the run-in visit (visit 1) to the end-of-trial visit (visit 11).

b Pain impact will be assessed by subjects in e-Diary on both a daily and a weekly basis.

6.1 Activities between Clinic Visits

In this trial, a menstrual cycle is considered the period between day 7 of return of menses (RM+7) in a cycle until the following RM+7. Visits on RM+7 can be scheduled on RM+6-10, i.e. day 6 to day 10 of return of menses. Similarly, visits on LH+7 can be scheduled on LH+6-9, i.e. 6-9 days after LH surge, which is either assessed by the subject using LH surge kits at home or estimated by the site staff based on subject's cycle length. If subjects do not have menstrual bleeding in a cycle during the treatment and follow-up period, the RM+7 visit in that cycle must be arranged within 35 days of the last RM+7 visit.

The review of the e-Diary, which covers compliance with e-Diary completion and analgesic use should be performed by site staff regularly between clinic visits.

Contraception counselling and condoms will be offered to subjects as needed throughout the trial.

6.1.1 Premature Discontinuation

In case of premature discontinuation, an end-of-treatment visit (see section 6.4.6) should be arranged as soon as possible (preferably within 7 days of the last ring removal). Subjects who are prematurely discontinued from the treatment due to adverse events will be asked to attend an end-of-trial visit (see section 6.5.1) within 2 weeks of the end-of-treatment visit. If subjects are discontinued for other reasons, the end-of-treatment and end-of-trial visits can coincide.

If a discontinued subject is found with an ongoing adverse event classified as serious or considered to have a reasonable possible causality to the IMP at their last trial visit, the site staff should follow up until the event is resolved (see section 8.6).

6.2 Screening

Potential participants will be scheduled to come to the clinic for the screening assessments. The screening period includes a wash-out period of approximately one month (only applicable to subjects currently using some hormonal products such as contraceptives [c]) and a run-in period of two complete menstrual cycles (cycles -2 and -1, applicable to all subjects).

In case of technical issues at the start of the run-in period, subjects are allowed to re-start cycle -2 after undergoing all procedures at visit 2 except for PGIS and LH surge test reminders. Subjects that screen fail due to the temporary trial hold during the coronavirus disease 2019 (COVID-19) pandemic may be re-screened. In this case, subjects need to repeat the two run-in cycles, but can be waived from the echocardiography assessment as applicable.

6.2.1 Wash-out Period (As Applicable)

Subjects who are currently using some hormonal products (including GnRH antagonists, aromatase inhibitors, danazol and hormonal contraceptives such as combined oral contraceptive pill, progestin-only pill, transdermal patch and contraceptive ring) may be eligible for the trial if they have completed the wash-out period. In this case, subjects need to sign the informed consent(s) before they discontinue those products. Discontinuation of the products should follow the labelling (e.g. completing the current cycle of contraceptives before wash-out).

Subjects requiring wash-out will not be provided with e-Diary or rescue analgesics until the completion of the wash-out period, i.e. at the run-in visit.

The following must take place if a wash-out period is required:

- Signed and dated written informed consent(s)
  - Mandatory for the informed consent covering the participation of the trial [*note*: this must be obtained prior to any trial-related procedures]
  - Optional for the informed consent covering the cell-free DNA/microRNA and pharmacogenetic sampling [*note*: this needs to be obtained prior to the sampling]
  - Optional for the informed consent covering the patient interview [*note*: this needs to be obtained prior to the patient interview]
- Allocation of a screening number
- Check of inclusion and exclusion criteria (those which are possible to check at this stage)
- Recording of use of any concomitant medications (within the last 3 months prior to the signed informed consent for participation in the trial, i.e. the main informed consent)
- Recording of adverse events (from the date of signed main informed consent)
- Reminding the subject to attend the RM+7 visit after completion of the wash-out period

6.2.2 Visit 1 (Start of Run-in)

Subjects will attend visit 1 (run-in visit), scheduled on RM+6-10 of a cycle prior to cycle -2. Some assessments listed below can be performed before visit 1 but not before the wash-out visit. Subjects

must receive a signed copy of informed consent form(s) before any trial-related procedures.

The following must take place for those subjects who do NOT require a wash-out period and can be performed either before or at visit 1 (i.e., before subject's entry into run-in):

- Signed and dated written informed consent(s)
  - Mandatory for the informed consent covering the participation of the trial [*note*: this must be obtained prior to any trial-related procedures]
  - Optional for the informed consent covering the cell-free DNA/microRNA and pharmacogenetic sampling [*note*: this needs to be obtained prior to the sampling]
  - Optional for the informed consent covering the patient interview [*note*: this needs to be obtained prior to the patient interview]
- Allocation of a screening number

The following procedures must be performed for all subjects either before or at visit 1 (i.e., before subject's entry into run-in):

- Asking subjects to score the worst endometriosis-related pain on the NRS on paper based on a recall of experience in the past menstrual cycle (see Appendix 1, a score ≥5 for eligibility)
- Asking subjects to complete the electronic Columbia-Suicidal Severity Rating Scale (eC-SSRS)
- Check of inclusion and exclusion criteria (those which are possible to check at this stage)
- Demographics (age, ethnicity, race)
- Collection of the following data:
  - Medical history
  - Menstrual history
  - Reproductive history
- Body measurement (body weight, height) [*note*: these are used for calculation of BMI]
- Vital signs
- Physical examination
- Gynecological examination
- Cervical swab [*note*: results must be negative]
- Transvaginal ultrasound
- Urine pregnancy test [*note*: results must be negative. If positive, a serum test must be done]
- Urine drug screen
- Urinalysis

The following procedures will be performed at visit 1 if subjects are considered eligible for the trial based on the inclusion and exclusion criteria assessed at this time point:

- Training the subject for e-Diary use after helping her with e-Diary installation on her own phone or providing her with an e-Diary device
- Confirmation of the start date and, if applicable, stop date of menses in the current cycle

- Recording of use of any concomitant medications (within the last 3 months prior to the signed informed consent for participation in the trial, i.e. the main informed consent, or from last visit)
- Recording of adverse events (from the date of signed main informed consent or last visit)
- Dispensing / prescription of rescue analgesics
- Dispensing of condoms and reminding the subject to use proper contraception
- Dispensing of LH surge kits and giving instructions on testing LH surge during cycle -1
- Reminding the subject to bring back all used and unused ibuprofen to the next visit
- Reminding the subject to attend the RM+7 visit of cycle -2

6.2.3 Visit 2 (RM+7 of Cycle -2)

Subjects will attend visit 2, scheduled on RM+6-10 of cycle -2.

The following must take place at the visit:

- e-Diary review and ensure that the subject is still eligible for participation in the trial
- Urine pregnancy test [*note*: results must be negative. If positive, a serum test must be done]

The following procedures will be performed if subjects are considered eligible for the trial based on the inclusion and exclusion criteria assessed at this time point:

- Ensure the completion of the PGIS scale by the subject
- Confirmation of the start date and, if applicable, stop date of menses in the current cycle
- Drug accountability of ibuprofen as applicable
- Recording of use of any concomitant medications
- Recording of adverse events
- Dispensing / prescription of rescue analgesics
- Dispensing of condoms and reminding the subject to use proper contraception
- Reminding the subject to test LH surge during cycle -1 as applicable
- Reminding the subject to complete the e-Diary before bedtime every day
- Reminding the subject to bring back all used and unused ibuprofen to the next visit
- Reminding the subject to attend the LH+7 visit of cycle -1

6.2.4 Visit 3 (LH+7 of Cycle -1)

Subjects will attend visit 3, scheduled on LH+6-9 of cycle -1. Subjects will be required to fast overnight (no food or drinks except for water after midnight) before the visit.

The following must take place at the visit:

- e-Diary review and ensure that the subject is still eligible for participation in the trial [*note*: only compliance can be checked at this visit]
- Urine pregnancy test [*note*: results must be negative. If positive, a serum test must be done]

The following procedures will be performed if subjects are considered eligible for the trial based on the inclusion and exclusion criteria assessed at this time point:

- ECG [*note*: this can be performed anytime during cycle -1 but results must be available before randomization. ECG must be performed before blood sampling when applicable]
- Echocardiography [*note*: this can be performed anytime during cycle -1 but results must be available before randomization]
- Blood collection for analysis of:
  - Clinical chemistry and hematology parameters [*note*: the result must be available prior to randomization]
  - Endocrine panel (estradiol, progesterone, prolactin, TSH and IGF-1) [*note*: the result must be available prior to randomization]
  - Bone turnover markers (s-CTx and s-PINP)
  - Endometriosis biomarkers including but not limited to VEGF, PlGF, IL-6 and sFlt-1; if the subject has provided a separate informed consent, additional samples for potential analyses of cell-free DNA and microRNA will be collected (section 7.3.1)
- Drug accountability of ibuprofen as applicable
- Recording of use of any concomitant medications
- Recording of adverse events
- Dispensing / prescription of rescue analgesics
- Dispensing of condoms and reminding the subject to use proper contraception
- Reminding the subject to complete the e-Diary before bedtime every day
- Reminding the subject to bring back all used and unused ibuprofen to the next visit
- Reminding the subject to attend the RM+7 visit of cycle -1

6.3 Randomization

6.3.1 Visit 4 (RM+7 of Cycle -1)

Subjects will attend visit 4, scheduled on RM+6-10 of cycle -1.

The following must take place prior to randomization:

- e-Diary review and ensure that the subject is still eligible for participation in the trial
- Urine pregnancy test [*note*: results must be negative. If positive, a serum test must be done]
- Urine drug screen
- Vital signs
- Completing the questionnaire for impulsive-compulsive disorders (QICD) based on the subject's verbal responses
- Ensure the completion of the eC-SSRS by the subject
- Check those inclusion and exclusion criteria that were not possible during screening

If the subject fulfils all inclusion and exclusion criteria, she will proceed to randomization:

- Randomization, i.e. being assigned to a unique subject number in the e-CRF and thereby allocated to placebo vaginal ring or quinagolide vaginal ring dose load 360, 720 or 1080 µg

The following will be performed for eligible subjects before insertion of the ring:

- Ensure the completion of the EHP-30 questionnaire by the subject
- Ensure the completion of the PGIS scale by the subject
- Completing the first part of B&B scale based on the subject's verbal responses
- Pelvic examination for the second part of B&B scale (see section 7.2.2.17.4.12)
- Investigator completing the second part of B&B scale based on findings from an examination of pelvic tenderness and induration (see section 7.2.2.1)

Once the above has been completed, the following must be performed:

- Confirmation of the start date and, if applicable, stop date of menses in the current cycle
- Access the IRT system to obtain an identification number for a vaginal ring to dispense
- Subject will be instructed to insert the assigned vaginal ring in the upper part of the vagina. Supervision by the site staff can be provided if needed
- Ensure the completion of the ring acceptability questionnaire (simplified version, with only one question about ring insertion) by the subject

Finally, the following must be done before the subject leaves the clinic:

- Drug accountability of ibuprofen as applicable
- Recording of use of any concomitant medications
- Recording of adverse events
- Dispensing / prescription of rescue analgesics
- Dispensing of condoms and reminding the subject to use proper contraception
- Reminding the subject to complete the e-Diary before bedtime every day
- Reminding the subject to bring back all used and unused ibuprofen to visit 6
- Reminding the subject to attend the next visit, scheduled within 1-5 days of ring insertion

6.4 Treatment

6.4.1 Visit 5 (Within 1-5 days of Visit 4)

Subjects will attend visit 5, scheduled within 1-5 days of visit 4.

The following must take place at the visit:

- Vital signs [*note*: vital signs must be performed before blood sampling]
- Blood collection for analysis of
  - Plasma concentration of quinagolide and metabolites
  - Pharmacogenetics (only if the subject has provided a separate informed consent)

- e-Diary review
- Recording of use of any concomitant medications
- Recording of adverse events
- Dispensing of condoms and reminding the subject to use proper contraception
- Reminding the subject to complete the e-Diary before bedtime every day
- Reminding the subject to bring back all used and unused ibuprofen to the next visit
- Reminding the subject to attend the RM+7 visit of cycle 1

6.4.2 Visit 6 (RM+7 of Cycle 1)

Subjects will attend visit 6, scheduled on RM+6-10 of cycle 1.

The following must take place before ring insertion / removal:

- Ensure the completion of the EHP-30 questionnaire by the subject
- Urine pregnancy test [*note*: results must be negative. If positive, a serum test must be done]
- Blood collection for analysis of:
  - Plasma concentration of quinagolide and metabolites

Once the above has been completed, the following must be performed:

- e-Diary review
- Confirmation of the start date and, if applicable, stop date of menses in the current cycle
- Access the IRT system to obtain an identification number for a new vaginal ring to dispense
- Removal of the used ring and insertion of the new ring by the subject. Supervision by the site staff can be provided if needed
- Ensure the completion of the ring acceptability questionnaire (full version) by the subject
- Drug accountability of the ring and ibuprofen as applicable
- Recording of use of any concomitant medications
- Recording of adverse events
- Dispensing / prescription of rescue analgesics
- Dispensing of condoms and reminding the subject to use proper contraception
- Reminding the subject to complete the e-Diary before bedtime every day
- Reminding the subject to bring back all used and unused ibuprofen to the next visit
- Reminding the subject to attend the RM+7 visit of cycle 2

6.4.3 Visit 7 (RM+7 of Cycle 2)

Subjects will attend visit 7, scheduled on RM+6-10 of cycle 2.

The following must take place before ring insertion / removal:

- Ensure the completion of the EHP-30 questionnaire by the subject

- Ensure the completion of the eC-SSRS by the subject
- Urine pregnancy test [*note*: results must be negative. If positive, a serum test must be done]

Once the above has been completed, the following must be performed:

- e-Diary review
- Confirmation of the start date and, if applicable, stop date of menses in the current cycle
- Access the IRT system to obtain an identification number for a new vaginal ring to dispense
- Removal of the used ring and insertion of the new ring by the subject. Supervision by the site staff can be provided if needed
- Ensure the completion of the ring acceptability questionnaire (full version) by the subject
- Drug accountability of the ring and ibuprofen as applicable
- Recording of use of any concomitant medications
- Recording of adverse events
- Dispensing / prescription of rescue analgesics
- Dispensing of condoms and reminding the subject to use proper contraception
- Dispensing of LH surge test kits and giving instructions on testing LH surge during cycle 4
- Reminding the subject to complete the e-Diary before bedtime every day
- Reminding the subject to bring back all used and unused ibuprofen to the next visit
- Reminding the subject to attend the RM+7 visit of cycle 3

6.4.4 Visit 8 (RM+7 of Cycle 3)

Subjects will attend visit 8, scheduled on RM+6-10 of cycle 3.

The following must take place before ring insertion / removal:

- Ensure the completion of the EHP-30 questionnaire by the subject
- Urine pregnancy test [*note*: results must be negative. If positive, a serum test must be done]
- Blood collection for analysis of:
  - Plasma concentration of quinagolide and metabolites

Once the above has been completed, the following must be performed:

- e-Diary review
- Confirmation of the start date and, if applicable, stop date of menses in the current cycle
- Access the IRT system to obtain an identification number for a new vaginal ring to dispense
- Removal of the used ring and insertion of the new ring by the subject. Supervision by the site staff can be provided if needed
- Ensure the completion of the ring acceptability questionnaire (full version) by the subject
- Drug accountability of the ring and ibuprofen as applicable
- Recording of use of any concomitant medications
- Recording of adverse events

- Dispensing / prescription of rescue analgesics
- Dispensing of condoms and reminding the subject to use proper contraception
- Reminding the subject to test LH surge during cycle 4 as applicable
- Reminding the subject to complete the e-Diary before bedtime every day
- Reminding the subject to bring back all used and unused ibuprofen to the next visit
- Reminding the subject to attend the LH+7 visit of cycle 4

6.4.5 Visit 9 (LH+7 of Cycle 4)

Subjects will attend visit 9, scheduled on LH+6-9 of cycle 4. Subjects will be required to fast overnight (no food or drinks except for water after midnight) before the visit.

The following must take place at the visit:

- Urine pregnancy test [*note*: results must be negative. If positive, a serum test must be done]
- Blood collection for analysis of:
  - Endocrine panel (estradiol, progesterone, prolactin, TSH and IGF-1)
  - Bone turnover markers (s-CTx and s-PINP)
  - Plasma concentration of quinagolide and metabolites
  - Endometriosis biomarkers including but not limited to VEGF, PlGF, IL-6 and sFlt-1; if the subject has provided a separate informed consent, additional samples for potential analyses of cell-free DNA and microRNA will be collected (section 7.3.1)
- e-Diary review
- Drug accountability of ibuprofen as applicable
- Recording of use of any concomitant medications
- Recording of adverse events
- Dispensing / prescription of rescue analgesics
- Dispensing of condoms and reminding the subject to use proper contraception
- Reminding the subject to complete the e-Diary before bedtime every day
- Reminding the subject to bring back all used and unused ibuprofen to the next visit
- Reminding the subject to attend the RM+7 visit of cycle 4

6.4.6 Visit 10 (End-of-Treatment / RM+7 of Cycle 4)

If subjects attend all scheduled visits and complete the treatment, an end-of-treatment visit (visit 10) will be scheduled on RM+6-10 of cycle 4. If subjects are discontinued from the treatment prematurely, an end-of-treatment visit with the following end-of-treatment assessments should be scheduled as soon as possible (preferably within 7 days of the last ring removal).

The following must take place first:

- Ensure the completion of the EHP-30 questionnaire by the subject
- Ensure the completion of the PGIS scale by the subject

- Ensure the completion of the PGIC scale by the subject
- Completing the first part of B&B scale based on the subject's verbal response
- Completing the questionnaire for impulsive-compulsive disorders (QICD) based on the subject's verbal responses
- Ensure the completion of the eC-SSRS by the subject

Once the above has been completed, the following must be performed:

- Vital signs [*note*: vital signs must be performed before blood sampling]
- ECG [*note*: this can be done within ±2 weeks of the visit and must be performed before blood sampling when applicable]
- Echocardiography [*note*: this can be done within ±2 weeks of the visit]
- Physical examination
- Gynecological examination
- Transvaginal ultrasound
- Investigator completing the second part of B&B scale based on findings from an examination of pelvic tenderness and induration (see section 7.2.2.1)
- Urine pregnancy test [*note*: this is performed prior to ring insertion / removal. Results must be negative. If positive, a serum test must be done]
- Urinalysis
- Blood collection for analysis of:
  - Plasma concentration of quinagolide and metabolites [*note*: this is performed prior to ring insertion / removal]
  - Clinical chemistry and hematology parameters
- Removal of the used ring. Supervision by the site staff can be provided if needed
- Ensure the completion of the ring acceptability questionnaire (full version) by the subject

Lastly, the following must take place at this visit:

- e-Diary review
- Confirmation of the start date and, if applicable, stop date of menses in the current cycle
- Drug accountability of the ring and ibuprofen as applicable
- Recording of use of any concomitant medications
- Recording of adverse events
- Completion the end-of-treatment question where subjects will be asked which treatment (placebo or quinagolide) they believe they have received
- Completion of end-of-treatment form

For subjects who have completed the treatment, the following must be performed:

- Dispensing / prescription of rescue analgesics
- Dispensing of condoms and reminding the subject to use proper contraception
- Reminding the subject to complete the e-Diary before bedtime every day

- Reminding the subject to bring back all used and unused ibuprofen to the next visit
- Reminding the subject to attend the RM+7 visit of cycle 5

For subjects who are prematurely discontinued from the treatment due to adverse events, the next visit is the end-of-trial visit (see section 6.5.16.5.1) scheduled within 2 weeks. For subjects who are prematurely discontinued from the treatment for other reasons, the completion of end-of-treatment assessments outlined in this section and end-of-trial assessments listed in section 6.5.1 are required at their last trial visit.

6.5 Follow-up

6.5.1 Visit 11 (End-of-Trial / RM+7 of Cycle 5)

If subjects attend all scheduled visits, an end-of-trial visit (visit 11) will be scheduled on RM+6-10 of cycle 5. If subjects are prematurely discontinued from the treatment due to adverse events, subjects will be asked to attend an end-of-trial visit within 2 weeks of the end-of-treatment visit. If subjects are prematurely discontinued for other reasons, an end-of-trial visit can be scheduled on the same day of the end-of-treatment visit.

The following end-of-trial assessments must take place at the subject's last visit:

- Urine pregnancy test [*note*: results must be negative. If positive, a serum test must be done]
- Blood collection for analysis of:
  - Clinical chemistry and hematology parameters
- e-Diary review
- Uninstallation of e-Diary app or collection of e-Diary device as applicable
- Confirmation of the start date and, if applicable, stop date of menses in the current cycle
- Drug accountability of ibuprofen as applicable
- Recording of use of any concomitant medications
- Recording of adverse events
- Completion of the end-of-trial form

7 TRIAL ASSESSMENTS

7.1 Assessments Related to Primary Endpoint

7.1.1 Endometriosis-related Pain

Endometriosis-related pain, i.e. pain located in the abdominal-pelvic area and the lower back area, will be assessed by subjects in an e-Diary on a daily basis from run-in to follow-up (cycle -2 to cycle 5). An illustration of a female body with the abdominal-pelvic area and lower back area circled will be presented in the instructions (see Figure 7-1). Subjects will be asked to score based on the worst pain they experienced in the circled areas during the preceding 24 hours on a self-administered 11-point NRS and note it down in the e-Diary before bedtime[e] every night. The daily diary will be accessible from 8 pm to 2 am every day.

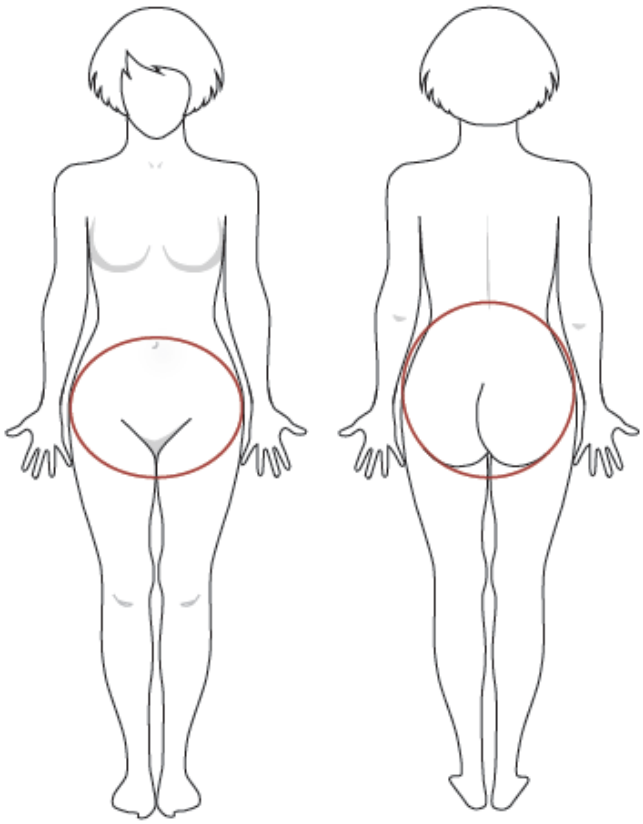


Figure 7-1 Location of Endometriosis-related Pain

[e] When subjects have irregular sleep schedules, they shall enter data between 8 pm and 2 am rather than at bedtime.

Instructions and the question to be answered are:

Please think about the **worst** endometriosis-related pain you experienced in the past 24 hours and rate it on a scale from 0 to 10 where 0 is 'no pain' and 10 is 'worst imaginable pain'. Please do not include pain from sexual intercourse.

1. Please rate your **worst** endometriosis-related pain in the past 24 hours (including pelvic pain, abdominal pain, or lower back pain, whichever is the worst).

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No pain										Worst imaginable pain

The mean of the daily NRS scores obtained during the two run-in menstrual cycles (cycles -2 and -1) for endometriosis-related pain will be considered baseline.

If the subject did not complete the daily diary the day before, a question related to reasons for no data entry will be asked at the end of the diary.

The question to be answered is:

If the subject did not answer the diary yesterday:

14. Please let us know why you did not complete the diary yesterday.
☐ I was in too much pain from endometriosis
☐ I forgot
☐ Other reason

The answer to this question will be used to impute scores for missing data (section 9.6.1). The complete e-Diary including instructions and questions are available in Appendix 1.

7.2 Assessments Related to Secondary Endpoints

7.2.1 Assessments Related to Secondary Endpoints in e-Diary

Subjects will be instructed to complete the e-Diary on a daily basis from run-in to follow-up (cycle -2 to cycle 5). In addition to endometriosis-related pain, they should assess the following items during the past 24 hours before bedtime every day in the e-Diary: vaginal bleeding, occurrence of sexual intercourse and dyspareunia (if applicable), and analgesic use. The impact of endometriosis-related pain will be assessed by subjects on both a daily and a weekly basis. Of these assessments, questions concerning endometriosis-related pain, vaginal bleeding, occurrence of sexual intercourse and pain impact are components of the newly developed PRO tool Women's Endometriosis Diary.

The complete e-Diary including instructions and questions are available in Appendix 1.

7.2.1.1 Dysmenorrhea and Non-menstrual Pelvic Pain

Dysmenorrhea is defined as "endometriosis-related pain on days with menstrual bleeding", while non-menstrual pelvic pain is defined as "endometriosis-related pain on days with no menstrual bleeding". The question on endometriosis-related pain (Question 1) is available in section 7.1.1.

If subjects have any vaginal bleeding, they will be asked whether it is menstrual bleeding or not. Based on the woman's subjective impression of whether she has menstrual bleeding or not, the daily NRS score for endometriosis-related pain will be assigned to dysmenorrhea or to non-menstrual pelvic pain. The questions on vaginal bleeding and menstrual bleeding (Question 9 and Question 11) are available in section 7.2.1.4.

The mean of the daily NRS scores obtained during the two run-in menstrual cycles (cycles -2 and -1) for dysmenorrhea and for non-menstrual pelvic pain, respectively, will be considered baseline scores.

7.2.1.2 Dyspareunia and Frequency of Avoiding Sexual Intercourse due to Expected Pain

Occurrence of sexual intercourse ("yes" or "no") will also be recorded in the e-Diary on a daily basis from run-in to follow-up (cycle -2 to cycle 5). In case of sexual intercourse, subjects will be asked to score the worst pain they experienced during or after the intercourse (dyspareunia) on the NRS. In case of no sexual intercourse, subjects will be asked if it is due to expected pain ("yes" or "no").

The questions to be answered are

2. Did you have sexual intercourse in the past 24 hours?
   ☐ No
   ☐ Yes

If the subject did not have sexual intercourse in the past 24 hours:

3. Did you **avoid** sexual intercourse in the past 24 hours because of expected endometriosis-related pain?
   ☐ No
   ☐ Yes

If the subject had sexual intercourse in the past 24 hours:

4. Please rate your **worst** pain during or after sexual intercourse in the past 24 hours.

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No pain										Worst imaginable pain

The mean of the NRS scores obtained for dyspareunia on the days with sexual intercourse and the frequency of avoiding sexual intercourse during the two run-in menstrual cycles (cycles -2 and -1) will be considered baseline of the respective endpoint.

7.2.1.3 Pain Impact

Daily Pain Impact on Functioning

Subjects will assess the worst impact of the endometriosis-related pain on different aspects of functioning during the past 24 hours on the NRS before bedtime every day in a daily e-Diary from run-in to follow-up (cycle -2 to cycle 5).

The questions to be answered are

5. How did your endometriosis-related pain limit your sitting, standing and walking in the past 24 hours?

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No limitations on activities										Unable to do activities

6. How did your endometriosis-related pain limit your daily activities around the house, such as doing chores, laundry, cooking, washing dishes, or cleaning in the past 24 hours?

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No limitations on activities										Unable to do activities

7. How did your endometriosis-related pain limit your work/school in the past 24 hours?

☐ Not applicable, no work or school in the past 24 hours.

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No limitations on activities										Unable to do activities

8. How did your endometriosis-related pain limit your social activities with family or friends in the past 24 hours?

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No limitations on activities										Unable to do activities

The average of the mean daily NRS scores obtained for the worst endometriosis-related pain impact on different aspects of functioning during the two run-in menstrual cycles (cycles -2 and -1) will be considered baseline.

Weekly Pain Impact on Functioning

In addition to this daily item, a modified EHP-30 pain impact domain consisting of the first 11 questions of the core EHP-30 questionnaire and an additional work item will be completed by subjects on a weekly basis in the e-Diary. The weekly pain impact questionnaire measures the frequency of the endometriosis-related pain impact on various aspects of functioning such as doing house chores, standing, sitting and walking during the past week, with the response levels of never, rarely, sometimes, often and always (see Figure 7-2). The weekly diary will be accessible from 8 pm on Sundays to 2 am on Tuesdays.

During the **last week**, because of your endometriosis, how often have you...

	Never	Rarely	Sometimes	Often	Always
1. Been unable to go to social events because of the pain?	☐	☐	☐	☐	☐
2. Been unable to do jobs around the house because of the pain?	☐	☐	☐	☐	☐
3. Found it difficult to stand because of the pain?	☐	☐	☐	☐	☐
4. Found it difficult to sit because of the pain?	☐	☐	☐	☐	☐
5. Found it difficult to walk because of the pain?	☐	☐	☐	☐	☐
6. Found it difficult to exercise or do the leisure activities you would like to do because of the pain?	☐	☐	☐	☐	☐
7. Lost your appetite and/or been unable to eat because of the pain?	☐	☐	☐	☐	☐
8. Been unable to sleep properly because of the pain?	☐	☐	☐	☐	☐
9. Had to go to bed/lie down because of the pain?	☐	☐	☐	☐	☐
10. Been unable to do the things you want because of the pain?	☐	☐	☐	☐	☐
11. Felt unable to cope with the pain?	☐	☐	☐	☐	☐
12. Been unable to do jobs around the house, at work, or at school because of the pain?	☐	☐	☐	☐	☐

Figure 7-2 Modified Endometriosis Health Profile-30 (EHP-30) Pain Impact Domain

The additional work item (Question 12 in Figure 7-2) will only be used for validation of the weekly e-Diary. The secondary endpoint of changes in the weekly pain impact scores will be based on the original EHP-30 pain impact domain, i.e. the first 11 items. The mean of the weekly pain impact scores during the two run-in menstrual cycles (cycles -2 and -1) will be considered baseline.

7.2.1.4 Vaginal Bleeding Pattern

Subjects will register their vaginal bleeding pattern in the e-Diary every day from run-in to follow-up (cycle -2 to cycle 5). Subjects will first be asked if they have had any vaginal bleeding ("yes" or "no") during the past 24 hours. In case of any vaginal bleeding, subjects need to assess their bleeding volume as spotting (tiny amount of blood on underwear or panty liners), light bleeding (requiring 1-3 sanitary pads or tampons per day), moderate bleeding (requiring 4-6 sanitary pads or tampons per day) or heavy bleeding (requiring more than 6 sanitary pads or tampons per day). In addition, they need to indicate whether their bleeding is menstrual bleeding or not.

The questions to be answered are

9. Did you have vaginal bleeding in the past 24 hours?
   ☐ No
   ☐ Yes

If the subject had vaginal bleeding in the past 24 hours:

10. Please describe your bleeding in the past 24 hours.
   ☐ Spotting (tiny amount of blood on underwear or panty liners)
   ☐ Light (requiring 1-3 sanitary pads or tampons per day)
   ☐ Moderate (requiring 4-6 sanitary pads or tampons per day)
   ☐ Heavy (requiring more than 6 sanitary pads or tampons per day)

11. Was your bleeding related to your period (i.e., menstrual bleeding)?
   ☐ No
   ☐ Yes

Vaginal bleeding pattern is evaluated as the number of no bleeding, spotting, light bleeding, moderate bleeding and heavy bleeding days, the duration of menstrual and non-menstrual period, and the number of bleeding days during the non-menstrual period. The vaginal bleeding pattern during the two run-in menstrual cycles (cycles -2 and -1) will be considered baseline.

7.2.1.5 Analgesic Use

Rescue analgesics for endometriosis-related pain will be limited to ibuprofen and/or hydrocodone-acetaminophen in this trial. As a mild analgesic, ibuprofen will be provided in the form of 200 mg oral tablets to subjects for their use on an as-needed basis. The specific dosing regimen of ibuprofen will be advised by the investigator but the maximum amount is 800 mg (4 tablets) per dose and 3200 mg (16 tablets) per day in accordance with the label of prescription ibuprofen doses.[27]

Subjects will be instructed not to use other analgesics unless necessary. If there is a need to change analgesics, subjects should discuss with investigators, who may prescribe a strong rescue analgesic hydrocodone-acetaminophen at a dose of 5 mg hydrocodone plus 300 mg or 325 mg acetaminophen. Only oral tablet formulation of combined hydrocodone-acetaminophen (i.e. hydrocodone bitartrate/acetaminophen) is allowed in the present trial. The specific dosing regimen of hydrocodone-acetaminophen is decided by the investigator based on subjects' needs and tolerability in accordance with the labelling of the product.

After subjects' entry into the run-in period, investigators can either advise ibuprofen dosing regimen or prescribe hydrocodone-acetaminophen by taking subjects' preference and history of analgesic use into consideration. Investigators should not take the initiative to suggest any modifications to the subject's current rescue analgesic regimen.

Subjects will be asked to follow the investigators' instructions on the type(s) and dose(s) of rescue analgesics they can use and whether they can take different rescue analgesics at the same time. Use of any other analgesics for endometriosis-related pain is prohibited from the start of run-in to the end-of-trial (see section 4.3.1 for prohibited analgesics). Any prophylactic use of analgesics is also prohibited from the start of run-in to the end-of-trial.

In order for sites to perform drug accountability, subjects will be instructed to bring back any packages of used and unused ibuprofen to the site at each visit.

The type and amount of mild and/or strong rescue analgesics used will be reported by subjects using the e-Diary. If subjects indicate any use of other analgesics for endometriosis-related pain, the specific name and dose of the analgesics will be noted in the e-CRF, while subjects will report the number of tablets taken in the e-Dairy.

Use of analgesics for other reasons than endometriosis-related pain should not be recorded in the e-Diary. These medications will be captured in the e-CRF and the reasons for use will be inquired and documented for potential reporting of adverse events.

The questions to be answered are

The next questions ask about any use of **pain medication** in the past 24 hours.

12. Have you taken any medication to reduce your endometriosis-related pain in the past 24 hours?
☐ No
☐ Yes

13. Which medication did you take for your endometriosis-related pain in the past 24 hours? Please answer "No" or "Yes" for each medication listed below.

MOTRIN 200 mg
☐ No
☐ Yes
Hydrocodone-acetaminophen (prescribed)
☐ No
☐ Yes
Other
☐ No
☐ Yes

The subjects will be asked to specify the number of tablets taken for each medication where "yes" is selected: "Please specify the number of tablets you took."
<An arrow spin will be available to list the number of tablets for each medication where "yes" is ticked.>

The average percentage of days with rescue analgesic use, the average of the total and mean dose of rescue analgesic used by type during the two run-in menstrual cycles (cycles -2 and -1) will be considered baseline.

7.2.1.6 Responder Rate

Responder rate will be assessed as ≥30%, ≥50% and ≥70% reduction from baseline in mean daily NRS score for the worst endometriosis-related pain, dysmenorrhea, non-menstrual pelvic pain and the worst endometriosis-related pain impact. The mean of the daily NRS scores for endometriosis-related pain, dysmenorrhea, non-menstrual pelvic pain and scores for the worst endometriosis-related pain impact averaged over the two run-in menstrual cycles (cycles -2 and -1) will be considered baseline. Responder rate will be assessed for each cycle over 4 menstrual cycles.

7.2.2 Assessments Related to Secondary Endpoints at Clinic Visits

7.2.2.1 Biberoglu and Behrman (B&B) Scale

B&B scale is a widely used scale for endometriosis that consists of two parts, with the first part evaluating symptoms of endometriosis (i.e. different types of endometriosis pain) and the second part evaluating signs of endometriosis (see Appendix 1). It is available in English, but a Spanish translation can be administered if preferred by the subject.

The first part of B&B should be completed by trained trial coordinators based on subjects' verbal responses. In the first part, the subject will be asked to grade her pelvic pain (item A), dysmenorrhea (item B) and dyspareunia (item C) during the last menstrual cycle as none, mild, moderate or severe, corresponding to a score of 0-3. The criteria for being mild, moderate or severe are defined differently for each item. The total pelvic pain score is the sum of the three scores, i.e. A+B+C.

In the second part, the investigator should grade the subject's pelvic tenderness (item D) and induration (item E) based on findings from a pelvic examination as none, mild, moderate or severe, corresponding to a score of 0-3. Efforts should be made to ensure this assessment is performed by the same investigator for the same subject throughout the trial. The criteria for being mild, moderate or severe are defined differently for each item. The total physical sign pain score is the sum of the two scores, i.e. D+E. The total symptom and sign severity score is the sum of all five scores, i.e. A+B+C+D+E.

The trial coordinator and the investigator will be provided with different access codes to access separate parts of the B&B scale on an electronic tablet. To avoid bias in the assessment, the trial coordinator will only be able to access the first part of the scale for scoring while the investigator will only be able to access the second part of the scale. It is not allowed to have the same person administering both parts of the scale. In addition, the B&B scale should be completed independently from subjects' scorings in the e-Diary in this trial.

B&B will be administered at randomization and at cycle 4 (at visits 4 and 10). The first part of the B&B should always be completed before ring insertion / removal at both visits and also prior to non-PRO procedures at cycle 4. The scores obtained at randomization will be used as baseline.

7.2.2.2 Endometriosis Health Profile-30 (EHP-30) Questionnaire

The EHP-30 is a quality-of-life questionnaire validated in both English and Spanish for endometriosis patients. Subjects will complete the core part of the EHP-30 questionnaire consisting of 30 questions measuring the frequency of the endometriosis impact on their quality of life during the past 4 weeks, with five options of never, rarely, sometimes, often and always (see Appendix 1).

An electronic version of the EHP-30 will be completed by the subject prior to ring insertion at randomization, and prior to other non-PRO procedures at every cycle from cycle 1 to cycle 4 (at visits 4, 6, 7, 8 and 10).

The scores obtained at randomization (at visit 4) will be used as baseline.

7.2.2.3 Patient Global Impression of Severity (PGIS) Scale

PGIS is a static measure of the global treatment benefits from the patients' perspective. Subjects will be asked to evaluate endometriosis-related pain during the last menstrual cycle, during the menstrual bleeding days of the last menstrual cycle and during the non-menstrual-bleeding days of the last menstrual cycle. In addition, subjects will be asked to evaluate the impact of endometriosis-related pain on daily activities during the last menstrual cycle, during the menstrual bleeding days of the last menstrual cycle and during the non-menstrual-bleeding days of the last menstrual cycle. The scale is presented in Appendix 1. Subjects will complete the PGIS scale electronically at the site at cycle -2, prior to ring insertion at randomization and prior to other non-PRO procedures at cycle 4 (at visits 2, 4 and 10).

The scores obtained at cycle -2 (at visit 2) will be used specifically for the validation of the newly developed PRO tool: Women's Endometriosis Diary. The scores obtained at randomization (at visit 4) will be used as baseline.

7.2.2.4 Patient Global Impression of Change (PGIC) Scale

PGIC is a dynamic measure of the global treatment benefits from the patients' perspective. Subjects will be asked to evaluate change in endometriosis-related pain, change in dysmenorrhea and change of non-menstrual pelvic pain since initiation of treatment. In addition, subjects will also evaluate the change in the overall impact of endometriosis-related pain on daily activities, the change in endometriosis-related pain impact during their menstrual periods and change in the endometriosis-related pain impact during non-menstrual periods since initiation of treatment. The scale is presented in Appendix 1. Subjects will complete the PGIC scale electronically at the site prior to other non-PRO procedures at cycle 4 (at visit 10).

7.2.2.5 Plasma Concentration of Quinagolide and Metabolites

Blood samples for measurement of plasma concentration of quinagolide and its metabolites M1 and M2 will be collected within 1-5 days of first ring insertion, at RM+7 visits of cycles 1, 3 and 4 as well as at LH+7 visit of cycle 4 (at visits 5, 6, 8, 9 and 10). Blood samples should be taken prior to removal of the ring at RM+7 visits. The analysis of plasma concentration of quinagolide and its metabolites will be performed by means of a validated tandem mass spectrometry method.

7.2.2.6 Mid-luteal Phase Endocrine Parameters and Ovarian Function

Blood samples for the analysis of endocrine parameters, consisting of estradiol, progesterone, prolactin, TSH and IGF-1, will be collected during mid-luteal phase (i.e. LH+7) of cycles -1 and 4 (at visits 3 and 9). The proportion of subjects with serum levels of mid-luteal progesterone ≥25 nmol/L (7.9 ng/mL) will be calculated as evidence of ovulation.

The samples will be analyzed at a central laboratory. The investigator will review and evaluate the laboratory results. However, the results of progesterone, prolactin, TSH and IGF-1 after randomization will be blinded to investigators, site staff and Ferring clinical team. The laboratory report will be signed and dated by the investigator.

7.2.2.7 Bone Turnover Markers

Blood samples for the analysis of serum bone turnover markers, consisting of s-CTx and s-PINP, will be collected during mid-luteal phase (i.e. LH+7) of cycles -1 and 4 (at visits 3 and 9). Fasting overnight (no food or drinks except for water after midnight) is required for the blood sampling.

The samples will be analyzed at a central laboratory and data will be transferred directly to the database (i.e. not provided to the sites).

7.2.2.8 Electrocardiography (ECG)

The 12-lead ECG will be recorded within cycle -1 and at cycle 4 (around visits 3 and 10). ECG at screening can be performed anytime during cycle -1, e.g. at LH+7 visit (visit 3) but results must be available before randomization. The report must be reviewed, signed and dated by the investigator before randomization. Results at randomization will be used as baseline. ECG at cycle 4 can be performed within ±2 weeks of visit 10. ECG will be recorded with a calibrated ECG device after the subject has been in supine position for at least 5 minutes. ECG must be performed before blood sampling when applicable.

The parameters to be assessed are heart rate, PR interval, RR interval, QRS interval, QT interval and QTcF interval (i.e. QT correction according to the Fridericia's formula $QTcF = QT/RR^{0.33}$). ECG recordings will capture at least four QRS complexes, i.e. 3 evaluable RR intervals. All ECG recordings will be sent to a central cardiac laboratory for evaluation as normal or abnormal. If the results of central reading are abnormal, the investigator will evaluate whether the abnormal finding is clinically significant or not. Any occurrence of de- or re-polarization disorders (QT prolongation), arrhythmic disorders or other abnormalities will be assessed in comparison to the baseline.

ECG may be repeated for quality reasons and in this case the repeated assessment will be used for analysis. If subject demonstrates a prolongation of QTc interval ≥500 msec or a QTc interval change from baseline ≥60 msec, two additional ECG assessments should be acquired 2-5 minutes apart and all three ECG assessments should be re-evaluated by the central cardiac laboratory. If the averaged values from three consecutive ECG assessments indicate a prolongation of QTcF interval ≥500 msec or a QTcF interval change from baseline ≥60 msec as confirmed by the central cardiac laboratory, the subject should be discontinued from the treatment (see section 3.6.7).

7.2.2.9 Echocardiography

Echocardiography will be performed within cycle -1 and at cycle 4 (around visits 3 and 10). Echocardiography at screening can be arranged anytime during cycle -1, e.g. at LH+7 visit (visit 3) but results must be available prior to randomization. The report must be reviewed, signed and dated by the investigator before randomization. Echocardiography at cycle 4 can be performed within ±2 weeks of visit 10.

The 2-dimensional (2D) echocardiography and Doppler echocardiography will be used for assessment of valvular structure and function with a calibrated echocardiography device. For the same subject, all echocardiography assessments in this trial should be performed by the same type of echocardiography device at the same center.

After the subject has been in supine position for at least 5 minutes, the structure of mitral, tricuspid, aortic and pulmonary valves will be assessed semi-qualitatively by 2D echocardiography. Valvular regurgitation will be assessed by Doppler echocardiography. All echocardiography video clips at each visit will be sent to a central cardiac laboratory and stored for potential further evaluation. Assessment performed prior to randomization will be used as baseline and will be compared against assessments performed at cycle 4.

The echocardiography technicians and board-certified cardiologists from the central cardiac laboratory will evaluate each assessment as normal or abnormal according to American College of Cardiology / American Heart Association guidelines for valvular heart disease. If abnormal, the level of valvular regurgitation and valvular stenosis will be specified as mild, moderate or severe and valvular structure will be evaluated as well. Criteria are provided in a separate manual.

At cycle 4, any changes from baseline will be assessed by the primary cardiologist(s) at the central cardiac laboratory as significant or not significant. In case of significant change from baseline, irrespective of the change level, the echocardiogram will be re-evaluated and confirmed by a secondary cardiologist at the central cardiac laboratory. The degree of change in valve stenosis or regurgitation will be confirmed by quantitative analysis of gradients and valve area for stenotic lesions and by vena contracta width, jet area, and Doppler waveforms for regurgitant lesions. If the change is confirmed to be significant by the secondary cardiologist, the finding should be reported to the investigator who should evaluate the clinical significance of the finding in relation with clinical symptoms and other tests (e.g. ECG and vital signs). The subject will be discontinued from the treatment (see section 3.6.7) and will be referred to a cardiologist for further follow-up. A repeated echocardiography will be required and all video clips saved previously for the discontinued subject will be further evaluated by an external cardiologist for an independent evaluation of the findings and for a potential diagnosis of cardiac valvulopathy.

7.2.2.10 Impulse Control Disorder

A questionnaire adapted from a validated Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale[45] will be used to monitor any significant signs of pathological behaviors associated with impulse control disorder during the trial. The questionnaire has four primary questions concerning thoughts, urges/desires, behavior controls and engagement, each of which is applied to various behaviors associated with impulse control disorders, i.e. gambling, sex, buying, eating, performing tasks or hobbies, repeating simple activities and medication use. However, the original sub-question on medication use is not appropriate for this trial, as it focuses on the medication used for Parkinson's disease. Therefore this sub-question "taking your Parkinson's disease medications" has been deleted (see Appendix 1). The questionnaire uses a 5-point Likert scale (score 0-4) to measure the frequency of behaviors (never, rarely, sometimes, often and very often).

The questionnaire will be completed by trained trial coordinators based on subjects' verbal responses on an electronic tablet prior to randomization at cycle -1 (visit 4) and prior to other non-

PRO procedures at cycle 4 (visit 10). Subjects will be asked to answer questions based on behaviors occurring in any 4-week period during the trial at designated visits. An instruction sheet will be provided to trial coordinators with examples of the specific behaviors being assessed and a brief description of the Likert scale categories for frequency. Subjects indicating a score ≥2 for any sub-questions of Question 3 or a score ≥1 for any sub-questions of Question 4, i.e. a frequency of "sometimes" or even higher for any sub-questions of Question 3 regarding "Difficulty in controlling behaviors" or a frequency of "rarely" or even higher for any sub-questions of Question 4 regarding "Engage in activities", will be considered having potential behaviors associated with impulse control disorders. The behavior identified will be reported as an adverse event. In addition, if this is considered to be treatment-related by the investigator, the subject will be discontinued from the treatment (see section 3.6.7) and, if needed, will be referred to psychiatric counselling and will be followed up until symptoms are resolved.

7.2.2.11 Adverse Events

Adverse events will be recorded from the signing of informed consent(s) for participation in the trial until the end-of-trial visit. For each adverse event, the following parameters will be recorded by the investigator on the Adverse Event Log: description of event, date and time of onset, intensity, causal relation to IMP, action taken to IMP, other actions taken, seriousness of the adverse event, date and time of outcome, and outcome. A search for predefined preferred terms and reported terms will be conducted on all treatment-emergent adverse events to identify those potentially related to behaviors associated with impulse control disorders. See section 8.

7.2.2.12 Clinical Chemistry and Hematology Parameters

The following clinical chemistry and hematology parameters will be analyzed at a central laboratory:

CHEM-20: alanine transaminase, albumin, alkaline phosphatase, aspartate aminotransferase, bicarbonate, bilirubin direct, bilirubin total, blood urea nitrogen, calcium, chloride, cholesterol total, creatinine, gamma-glutamyl transpeptidase, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total protein, uric acid.

Complete Blood Count (CBC): red blood cells, red blood cell morphology, white blood cells, white blood cell morphology, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelets.

Blood samples will be drawn during mid-luteal phase (i.e. LH+7) of cycle -1 as baseline, at the end of treatment / cycle 4 and at the end of trial / cycle 5 (at visits 3, 10 and 11). The investigator will review the laboratory results and evaluate and document whether the abnormal results are clinically significant or not. The laboratory report will be signed and dated by the investigator.

7.2.2.13 Urinalysis

Urine samples for urinalysis will be collected before entry into run-in (before or at visit 1), and at the end of treatment / cycle 4 (at visit 10). Urinalysis will be performed from a sample of mid-stream urine by a dip-stick test at the local laboratory. Urinalysis parameters include protein, glucose, bilirubin, pH, nitrite, ketone, urobilinogen, blood, leukocytes and specific gravity. In case of any clinically significantly abnormal finding from the dipstick test, a microscopic test will be performed at the central laboratory. If the abnormal finding is confirmed, further examination may be initiated at the discretion of the investigator.

7.2.2.14 Ring Acceptability

The subject will be asked to evaluate the acceptability of the vaginal ring immediately after each time she has inserted and/or removed the ring at the clinic on RM+7 of cycle -1 to cycle 4 (at visits 4, 6, 7, 8 and 10).

At randomization (visit 4), a simplified version of the questionnaire with only one question about ring insertion (see Appendix 1) will be completed by the subject.

At RM+7 visits of cycle 1 to cycle 4 (visits 6, 7, 8 and 10), a full version of the ring acceptability questionnaire should be completed by the subject. The full version of the questionnaire consists of questions related to ring insertion / removal, any feeling of the ring while the ring is in the body, any feeling of the ring during sexual intercourse if applicable and any experience of ring falling out or breaking (see Appendix 1). If it is confirmed that the ring is broken upon removal, a technical complaint form should be completed. If it is noted that the ring has been out of the body for more than 24 hours during the cycle, a medication error should be reported.

The answer must be reviewed by the trial coordinator for the potential reporting of medication error before the subject leaves the clinic.

7.3 Assessment Related to Exploratory Endpoint

7.3.1 Potential Endometriosis Biomarkers

For all subjects, blood samples will be taken for potential endometriosis biomarkers during mid-luteal phase (i.e. LH+7) of cycles -1 and 4 (at visits 3 and 9). At each of these visits, approximately 1.5 mL of serum and 0.5 mL of platelet-free plasma will be collected and sent to a central laboratory for analysis of VEGF, PlGF, IL-6 and sFlt-1.

In addition, 2 mL of serum and plasma each will be collected from all subjects and stored for potential future analyses of other endometriosis biomarkers related to proteins (e.g. angiogenin).

All of the samples should be processed and stored in accordance with instructions provided in a separate laboratory manual. These exploratory data will not be provided to sites.

7.3.1.1 Optional Cell-free DNA and MicroRNA Analyses

If subjects have provided a separate written informed consent for genetic testing (see section 14.5), two additional blood samples will be collected at the same time points as detailed above for potential analyses of circulating cell-free DNA and microRNA. The informed consent for genetic testing signed by the subject must be obtained prior to the sampling.

All of the samples should be processed and stored in accordance with instructions provided in a separate laboratory manual. These exploratory data will not be provided to sites.

7.4 Other Assessments

7.4.1 Numerical Rating Scale (NRS) for Entry into Run-in

As part of the eligibility criteria check, all subjects will be asked to score the worst endometriosis-related pain from a recall of their experience during the past menstrual cycle (including days with menstrual bleeding and days with no menstrual bleeding) (see Appendix 1) before entry into run-in (before or at visit 1) on paper. Eligible subjects must have an NRS score of ≥5 to enter the run-in period.

7.4.2 Demographics

Demographic information will be obtained before entry into run-in (before or at visit 1), including the following: date of birth, ethnicity (Hispanic or Latino, Not Hispanic or Latino) and race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White).

7.4.3 Medical History

Any relevant medical history will be recorded before entry into run-in (before or at visit 1). This includes the year and method (laparoscopy or laparotomy) of endometriosis diagnosis, documentation of a biopsy (if performed), stage of endometriosis at diagnosis, anatomic location of endometriosis lesions (if available), history of previous surgical interventions (including method (laparoscopy or laparotomy), year and types of surgery (ablation of lesions, excision of lesions, lysis of adhesions or other)), and any surgical intervention for other gynecological conditions.

7.4.4 Menstrual History

Information about the menstrual history (average cycle length, average number of days with menstrual bleeding and amount of menstrual flow) will be obtained before entry into run-in (before or at visit 1). In addition, any history of irregular bleeding will be recorded.

7.4.5 Reproductive History

Information about the reproductive history will be obtained before entry into run-in (before or at visit 1). This includes number of pregnancies, number of live births and history of infertility (yes/no and if yes, reason for infertility).

7.4.6 Body Measurement

Body weight and height will be measured without shoes before entry into run-in (before or at visit 1). The results obtained will be used to calculate BMI.

7.4.7 Menstruation Dates

At each RM+7 visit throughout the trial, the site staff should confirm the subject's start date of menses in the current cycle, i.e. the first menstrual bleeding date (RM+1). If the subject has finished her menses when coming to the visit, the site staff should also confirm the stop date of menses in the current cycle, i.e. the last menstrual bleeding date.

7.4.8 Urine Pregnancy Test

A urine pregnancy test will be performed at each clinic visit (except for visit 5) throughout the trial. The test should always be performed before ring insertion / removal at RM+7 visits of the treatment period. If the test result is positive, a serum βhCG test must be performed. If both test results are positive, the subject will be discontinued from the trial.

7.4.9 Urine Drug Screen

A urine drug screen will be performed locally as part of eligibility check before entry into run-in (before or at visit 1) and prior to randomization at visit 4. The drug screen will be performed from fresh mid-stream urine for the determination of amphetamines / methamphetamine, barbiturates, benzodiazepines, cocaine, methylenedioxymethamphetamine, methadone, opiates, oxycodone, phencyclidine, tetrahydrocannabinol and tricyclic antidepressants. Subjects with a positive drug screen should be excluded unless the cause is from opioids or antidepressants that are medically indicated and prescribed by a physician.

7.4.10 Luteinizing Hormone Surge

LH kits will be dispensed to subjects at visits 1 and 7 for the assessment of LH surge during cycles -1 and 4. Instructions on LH surge testing and reminders of LH surge testing will be given.

7.4.11 Physical Examination

A complete physical examination will be performed before entry into run-in (before or at visit 1), and at end-of-treatment / cycle 4 (at visit 10). Information will be recorded for general appearance,

central and peripheral nervous system, head and neck (including ears, eyes, nose, mouth and throat), respiratory system, cardiovascular system, gastrointestinal system, lymphatic system, urinary system, musculoskeletal system and skin.

Before entry into run-in (baseline), each category will be evaluated as normal, abnormal not clinically significant or abnormal clinically significant. Abnormal clinically significant findings at baseline must be reported on the Medical History Log.

At cycle 4 / end-of-treatment, potential changes from baseline to cycle 4 or to end-of-treatment will be evaluated for each category. In case of changes, these will be evaluated as normal, abnormal not clinically significant or abnormal clinically significant. Abnormal clinically significant changes from baseline must be recorded as adverse events.

7.4.12 Gynecological and Pelvic Examination

A complete gynecological examination will be performed by the investigator before entry into run-in (before or at visit 1), and at end-of-treatment / cycle 4 (at visit 10). Information will be recorded for breast, external genitalia, vagina, cervix, uterus, uterine adnexa (including ovaries and fallopian tubes) and cul-de-sac.

Before entry into run-in (baseline), each category will be evaluated as normal, abnormal not clinically significant or abnormal clinically significant. Abnormal clinically significant findings at baseline must be reported on the Medical History Log.

At cycle 4 / end-of-treatment, potential changes from baseline to end-of-treatment will be evaluated for each category. In case of changes, these will be evaluated as normal, abnormal not clinically significant or abnormal clinically significant. Abnormal clinically significant changes from baseline must be recorded as adverse events.

In connection with the B&B scale scoring, an examination of pelvic tenderness and pelvic induration will be performed by the investigator at randomization and at cycle 4 (see section 7.2.2.1). The pelvic examination at cycle 4 is also part of the gynecological examination at cycle 4.

7.4.13 Cervical Swab

As part of eligibility check, a single swab will be obtained from the endocervical area before entry into run-in (before or at visit 1) for assessing gonorrhea and chlamydia. Subjects with positive test results must be excluded. Standard reporting and referral procedures at the sites will be followed in line with local regulations.

7.4.14 Transvaginal Ultrasound

A transvaginal ultrasound will be performed by an experienced sonographer before entry into run-in (before or at visit 1), and at end-of-treatment / cycle 4 (at visit 10). The transvaginal ultrasound will

assess uterus, endometrium and ovaries to evaluate endometrial thickness, number and size of endometrioma(s), ovarian cyst(s) and fibroid(s) if presented.

Endometrial thickness (composed of both layers of the endometrium) will be measured in the sagittal view of the uterus from the proximal and distal interfaces between the echogenic endometrium and the hypoechoic inner layer of the myometrium. Care should be taken not to include the presence of any fluid in the uterine cavity in calculating the endometrial thickness value. Endometrial thickness will be recorded in mm.

Endometrioma, fibroid and ovarian cyst will be recorded as observed or not. If observed, the number and size of endometrioma(s), fibroid(s) and ovarian cyst(s) should be recorded.

7.4.15 Vital Signs

Systolic and diastolic blood pressure as well as pulse will be measured before entry into run-in (before or at visit 1), prior to randomization at cycle -1, during cycle -1 and at end-of-treatment / cycle 4 (at visit 4, 5 and 10). Vital signs at randomization will be baseline. Blood pressure and pulse should be measured before blood sampling as applicable, by automated oscillometric device sequentially, first after the subject is in supine position for at least 3 minutes, then in seated position for at least 3 minutes, and then at 1 minute and at 3 minutes after standing. Changes in blood pressure will be calculated using the minimum standing measurement minus the seated measurement and minus the supine measurement, respectively.

The investigator will review the results of vital signs and evaluate and document whether the finding is clinically significant or not.

Before entry into run-in (before or at visit 1) and before randomization (at visit 4), subjects with a drop of 20 mmHg of systolic blood pressure or a drop of 10 mmHg of diastolic blood pressure from sitting to standing will be excluded from the trial.

At other visits (visits 5 and 10), a drop of 20 mmHg of systolic blood pressure or a drop of 10 mmHg of diastolic blood pressure from lying to standing or from sitting to standing is considered clinically significant and will be reported as adverse events.

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

The C-SSRS is a screening tool to assess the potential risk of suicidality. It is implemented in this trial to meet the US regulatory requirements for all neurologic drugs with central nervous system activity, even though quinagolide has not been shown to be associated with suicidal ideations during its marketing experiences of more than 20 years in Europe.

The electronic C-SSRS (eC-SSRS) will be self-administered through the interactive voice response (IVR) phone system (with a web portal as a back-up solution) before entry into run-in (before or at visit 1), prior to randomization at cycle -1, at cycles 2 and 4 (at visits 4, 7 and 10). The results of

eC-SSRS will be reviewed by investigators and delegated trial staff to assess the potential risk of suicidality, including suicidal ideations of type 4 (active suicidal ideations with some intent to act, without specific plan), suicidal ideations of type 5 (active suicidal ideations with specific plan and intent) and suicidal behavior.

Before entry into run-in (before or at visit 1), subjects having suicidal ideations of type 4 or type 5 during the past 12 months or having suicidal behavior during the past 5 years as identified by the eC-SSRS will be excluded from the trial. Prior to randomization at visit 4, subjects having suicidal ideations of type 4 or type 5 or having suicidal behavior since last e-CSSRS assessment will also be excluded from the trial. It is the investigator's responsibility to advise subjects excluded from the trial due to risk of suicidality to seek help from their own physicians or suicide prevention services.

During the treatment (at visits 7 and 10), subjects having suicidal ideations of type 4 or type 5 or having suicidal behavior as identified by the eC-SSRS should be referred to a mental health professional for further assessment and/or treatment. The decision on whether the treatment should be discontinued is to be taken by the investigator in consultation with the mental health professional to whom the subject is referred.

7.4.17 Concomitant Medication

The use of any concomitant medication within the last 3 months prior to informed consent for participation in the trial and throughout the trial will be recorded. Recording of concomitant medication other than ibuprofen and hydrocodone-acetaminophen will be performed at all visits. Any changes in concomitant medications or treatments must be recorded at each visit. Investigators' instructions for ibuprofen dosing and prescriptions of hydrocodone-acetaminophen will be recorded in the e-CRF.

7.4.18 Drug Accountability

For all vaginal rings, date and time of insertion and removal at the clinics will be recorded. Furthermore, the dates and amount of ibuprofen dispensed and returned will be recorded in the IRT system. Details on drug dispensing and accountability are provided in section 5.6.

7.4.19 End-of-Treatment Question

All subjects, irrespective of whether they completed the treatment or not, will be asked which treatment group (placebo or quinagolide) they believe they were randomized to at the end of treatment. The question can be phrased as "Do you think you were on a ring with study drug or a ring with placebo (i.e. no study drug)?"

7.4.20 End-of-Treatment Form

An end-of-treatment form should be filled in at the subject's end-of-treatment visit, irrespective of whether the subject completes the treatment or not. Completion / discontinuation status will be recorded, as well as date and reason for discontinuation in case the subject does not complete the treatment.

7.4.21 End-of-Trial Form

An end-of-trial form should be filled in at the subject's last visit, irrespective of whether the subject completes the trial or not. Completion / discontinuation status of the follow-up period will be recorded.

7.4.22 Optional Pharmacogenetic Analysis

If the subject has provided a separate written informed consent for genetic testing (see section 14.5), a sample of whole blood for extraction and analysis of DNA will be collected within 1-5 days of the first ring insertion during cycle 1 (at visit 5). The informed consent for genetic testing signed by the subject must be obtained prior to the sampling. All samples will be analyzed for the presence of polymorphisms in the cytochrome P450 2D6 (CYP2D6) gene, which codes for an enzyme involved in the metabolism of quinagolide.

Additional analysis of other enzymes involved in the elimination processes of quinagolide may be performed on samples from subjects who display quinagolide metabolite M1 concentrations at similar levels as the parent compound and on a comparable number of control samples from subjects with low levels of metabolites (M1<20% of quinagolide levels). Only enzymes responsible for the elimination processes (i.e. metabolism, transportation and excretion) of quinagolide will be analyzed. Results of the pharmacogenetic analysis will not be provided to the sites.

7.4.23 Optional Patient Interviews

A sub-group of 60 subjects including 5 non-completers from selected sites, if they have provided a separate informed consent, will be invited to a patient interview at the end of treatment to help determine the meaningful treatment benefit from the patients' perspective and to assess the content validity of the questions related to daily functioning in the e-Diary. The timing of the interview, i.e. within 2 weeks of subjects' completion of or discontinuation from the treatment (visit 10), allows for both subjects on active treatment and subjects on placebo to report their treatment experiences.

Subjects will be asked open-ended questions about the changes they have experienced since the start of the trial, and about the nature and relevance of these changes by following a semi-structured interview guide and a patient interview protocol.[46] In addition, the content validity of the daily functioning questions in the e-Diary will be assessed. The interviews will be conducted in English over the telephone by a trained interviewer from Evidera, a third-party CRO in the United States.

All interviews will last for approximately 2 hours, and will be audio-recorded. All subjects participating in the patient interview will be identified by using the same subject identification number of this trial to guarantee data protection. Both subjects and interviewers will be blinded to treatment allocation. Results of the patient interviews will be reported separately.

7.5 Handling of Biological Samples

Trial-specific laboratory manuals will be provided to the participating sites, describing in detail how to handle, store and transport the biological samples (blood) in this trial. All blood samples collected during the trial will be analyzed at central laboratories and will be destroyed within 2 years after reporting of the trial. Exceptions are the blood samples collected for potential future endometriosis biomarkers and for potential analyses of circulating cell-free DNA and microRNA; these will be stored for a maximum of 10 years after reporting of the trial prior to destruction in line with local regulations. For all biological samples collected in the trial, it applies that any analyses beyond those described in the protocol will be performed only after obtaining the required approvals. The processes related to handling of biological samples will be described in the informed consent documents, and the biobank / data protection legislations including local legislation will be adhered to.

8 ADVERSE EVENTS

8.1 Adverse Event Definition

An adverse event is any untoward medical occurrence in a subject participating in a clinical trial. It includes:

- Any unfavorable and unintended sign, symptom or disease temporally associated with the use of the IMP, whether or not considered to be caused by the IMP.
- Adverse events commonly observed and adverse events anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality, vital signs, ECG, echocardiography or finding from physical or gynecological examination including transvaginal ultrasound assessed as clinically significant by the investigator [*note*: findings from assessments and examinations done during the screening period are not adverse events, but are recorded as medical history.]
- Accidental injuries, reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures.

All adverse events will be coded by Ferring Pharmacovigilance using MedDRA (the MedDRA version will be documented).

Medication errors of IMP will be captured by ring acceptability questionnaire and/or a medication error form in the e-CRF.

8.2 Collection and Recording of Adverse Events

8.2.1 Collection of Adverse Events

The investigator must monitor the condition of the subject throughout the trial from the time of obtaining informed consent until the end-of-trial visit.

The sources of adverse events cover:

- The subject's response to questions about her health (a standard non-leading question such as "How have you been feeling since your last visit?" is asked at each visit).
- Symptoms spontaneously reported by the subject.
- Investigations and examinations where the findings are assessed by the investigator to be clinically significant changes or abnormalities.
- Other information relating to the subject's health becoming known to the investigator (e.g. hospitalization).

8.2.2 Recording of Adverse Events

The investigator must record all adverse events in the Adverse Event Log provided in each subject's e-CRF with information about:

- Adverse event
- Date and time of onset (time can be omitted, if applicable) [*note*: if date of onset of an event is the same as the date of informed consent or date of IMP administration, time is important and should not be omitted]
- Intensity
- Causal relationship to IMP
- Action taken to IMP
- Other action taken
- Date and time of outcome (time can be omitted, if applicable)
- Outcome
- Seriousness

Each of the items in the Adverse Event Log is described in detail in the following sections.

Adverse Event

Adverse events should be recorded as diagnoses, if available. If not, separate signs and symptoms should be recorded. One diagnosis / symptom should be entered per record.

If a subject suffers from the same adverse event more than once and the subject recovers in between the events, the adverse events should be recorded separately. If an adverse event changes in intensity, a worst-case approach should be used when recording the event, i.e. the highest intensity and the longest duration of the event.[f]

Note: A procedure is not an adverse event; the reason for conducting the procedure is. Hospitalization is not an adverse event; the reason for hospitalization is. Death is not an adverse event, but the cause of death is (an exception is sudden death of unknown cause, which is an adverse event).

Date and Time of Onset

The date of onset is the date when the first sign(s) or symptom(s) were first noted. If the adverse event is an abnormal clinically significant laboratory test or outcome of an examination, the onset

[f] Exception: if an adverse event with onset before the first IMP administration (i.e. a pre-treatment adverse event) changes in intensity after the IMP administration, this must be recorded as two separate events. The initial adverse event should be recorded with outcome "not recovered" and the date and time of outcome is when the intensity changed. The second adverse event should be recorded with date and time of onset when the intensity changed.

date is the date the sample was taken or the examination was performed.

Intensity

The intensity of an adverse event must be classified using the following 3-point scale:

Mild: Awareness of signs or symptoms, but no disruption of usual activity.

Moderate: Event sufficient to affect usual activity (disturbing).

Severe: Inability to work or perform usual activities (unacceptable).

Causal Relationship to IMP

The possibility of whether the IMP caused the adverse event must be classified as one of the following:

Reasonable possibility: There is evidence or argument to suggest a causal relationship between the IMP and the adverse event. The adverse event may occur as part of the pharmacological action of the IMP or may be unpredictable in its occurrence.

Examples:

- Adverse events that are uncommon but are known to be strongly associated with IMP exposure.
- Adverse events that are not commonly associated with IMP exposure, but the event occurs in association with other factors strongly suggesting causation, such as a strong temporal association with the IMP or the event recurs on rechallenge with the IMP.

No reasonable possibility: There is no reasonable evidence or argument to suggest a causal relationship between the IMP and the adverse event.

Examples:

- Known consequences of the underlying disease or condition under investigation.
- Adverse events common in the trial population, which are also anticipated to occur with some frequency during the course of the trial, regardless of IMP exposure.

Action Taken to IMP

The action taken to the IMP in response to an adverse event must be classified as one of the following:

- No change (medication schedule maintained or no action taken)
- Discontinued
- Interrupted

Other Action Taken

Adverse events requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the subject. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

If medication is administered to treat the adverse event, this medication should be entered in the Concomitant Medication Log.

Date and Time of Outcome

The date and time the subject recovered or died.

Outcome

The outcome of an adverse event must be classified as one of the following:

- Recovered (fully recovered or the condition has returned to the level observed at initiation of trial treatment)
- Recovered with sequelae (resulted in persistent or significant disability/incapacity)
- Recovering (the event is improving)
- Not recovered
- Fatal

8.3 Adverse Events of Special Interest

8.3.1 Dizziness / Pre-syncope

Dizziness or symptoms of pre-syncope (e.g. lightheadedness) will be reported as adverse events. Subjects will be instructed that they must lie down immediately if experiencing dizziness or any symptoms of pre-syncope. If symptoms are not resolved, they should contact the site staff as soon as possible for further instructions.

8.3.2 Syncope

Syncope is an adverse event of special interest in this trial and any cases of syncope will be reported as adverse events. Syncope is defined as "orthostatic collapse associated with an abrupt, transient, complete loss of consciousness and inability to maintain postural tone, with rapid and spontaneous recovery". In case of syncope, further evaluations including vital signs should be conducted as soon as the event is reported for the assessment of the causal relationship to the IMP.

8.3.3 Dysmenorrhea, Abdominal Pain, Pelvic Pain, Lower Back Pain and Dyspareunia

Endometriosis-related pain, i.e. pain located in the abdominal-pelvic area and the lower back area, will be assessed by the subject on the NRS scale on a daily basis. Dyspareunia will also be captured in the e-Diary in case of sexual intercourse. These data will be described as part of the primary and secondary endpoints based on the subjects' recordings in the diary.

Presence of dysmenorrhea, abdominal pain, pelvic pain or lower back pain related to endometriosis as well as menstrual cramp and dyspareunia are not to be reported as an adverse event unless it fulfils the criteria for an SAE.

8.3.4 Vaginal Bleeding

Vaginal bleeding pattern (no bleeding, spotting, light bleeding, moderate bleeding and heavy bleeding) will be evaluated by the subject in the e-Diary on a daily basis. These data will be described as a secondary endpoint based on the subjects' recordings in the diary. Abnormal vaginal bleeding (e.g. amenorrhea, oligomenorrhea, spotting or menstrual disorder) is not to be reported as an adverse event, unless there are any clinically significant changes from baseline that require medical or procedural intervention (e.g. prescription of tranexamic acid) or it fulfils the criteria for an SAE.

8.3.5 Ring Acceptability

Any feeling of the ring will be assessed by the subject in a ring acceptability questionnaire at the clinic. Discomfort in connection with the ring insertion and/or removal should not be reported as an adverse event unless it requires active management, i.e. discontinuation of IMP. The acceptability of vaginal rings constitutes a secondary endpoint and will be evaluated in detail based on the subjects' answers to the questionnaire. Any occurrence of ring expulsion or ring breaking will also be captured by ring acceptability questionnaire and should not be reported as an adverse event.

8.3.6 Vaginal Irritation and/or Vaginal Infection

Upon spontaneous reporting of vaginal irritation and/or vaginal infection including persistent vaginal itching, vaginal dryness, and/or vaginal discharge during the treatment period, an unscheduled gynecological examination can be performed. Vaginal irritation should be graded in accordance with Table 8-1. Clinically significant findings of vaginal irritation and/or vaginal

infection will be reported as an adverse event.

Table 8-1 Grading of Vaginal Irritation

VAGINAL IRRITATION				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Vaginal itching	Itching causing no, mild or moderate interference with usual social and functional activities	Itching causing inability to perform usual social and functional activities; may require intervention	NA	NA
Vaginal edema	Mild-moderate engorgement	Loss of rugae and friability	NA	NA
Vaginal erythema	Erythema <50% of vaginal surface	Erythema >50% of vaginal surface	NA	NA
Vaginal dryness	Dryness causing no or minimal interference with sexual function	Dryness causing greater than minimal interference with sexual function or causing frequent discomfort	NA	NA
Vaginal discharge by patient report	Mild to moderate increase in amount above baseline – no sanitary protection required	Profuse increase in discharge requiring pad or tampon use	NA	NA
Vaginal discharge as observed by investigator	No pooling	Pooling	NA	NA

Adapted from: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Addendum 1 (Female Genital Grading Table for Use In Microbicide Studies); November 2007.

8.4 Pregnancy and Pregnancy Outcome

If a pregnancy occurs, the IMP should be immediately stopped and Ferring Pharmacovigilance must be informed by mail to [redacted] within 3 calendar days. Pregnancy should be reported as a non-serious adverse event (for tracking purpose only, pregnancy in itself is not an adverse event). If a subject becomes pregnant during treatment or follow-up period and the conception date cannot be determined, an ultrasound will be performed as part of the standard pregnancy check-up to assess the conception date. The mother and the fetus must be followed up at least until the birth of the infant and 4-6 weeks after the birth of the infant. In general, the follow-up will include the course; duration and the outcome of the pregnancy as well as neonatal health. If a pregnancy results in an abnormal outcome (birth defect/congenital anomaly), this must be reported as an SAE to Pharmacovigilance. Abnormal pregnancy outcomes which the investigator and/or sponsor consider to be related to the IMP will be treated as expedited reports (see section 8.5.2).

8.5 Serious Adverse Events (SAEs)

8.5.1 Serious Adverse Event Definition

Serious Adverse Events during the Trial

An event is defined a serious adverse event if it:	Guidance
results in **death**	Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within four weeks after the treatment ends and irrespective of the causal relationship to the IMP. The death of a subject enrolled in a trial is *per se* not an event, but an outcome.
is **life-threatening**	The term life-threatening refers to an adverse event in which the subject was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death if it were more severe.
requires in-patient **hospitalization** or prolongation of existing hospitalization	The term hospitalization means that the subject was admitted to hospital or that existing hospitalization was extended as a result of an event. Hospitalization describes a period of at least 24 hours. Over-night stay for observation, stay at emergency room or treatment on an out-patient basis do not constitute a hospitalization. However, medical judgement must always be exercised and when in doubt the case should be considered serious (i.e. if case fulfils the criterion for a medically important event). Hospitalizations for administrative or social purposes do not constitute an SAE. Hospital admissions and/or surgical operations planned before trial inclusion are not considered adverse events, if the illness or disease existed before the subject was enrolled in the trial, provided that the condition did not deteriorate during the trial.
results in persistent or significant **disability/incapacity**	Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. In doubt, the decision should be left to medical judgement by the investigator.
is a **congenital anomaly/birth defect**	Congenital anomaly/birth defect observed in any offspring of the subject conceived during treatment with the IMP.
is an **important medical event**	Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are 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.

8.5.2 Collection, Recording and Reporting of Serious Adverse Events

SAE Reporting by the Investigator

All SAEs must be reported **immediately** to Ferring Pharmacovigilance as soon as it becomes known to the investigator and not later than within 24 hours of their knowledge of the occurrence of an SAE.

The investigator is responsible for submitting the completed SAE Report Form with the fullest possible details **within 3 calendar days** of his/her knowledge of the SAE.

SAE Report Form

The SAE Report Form is included in the e-CRF system, and must be completed and submitted according to the instructions provided on the form. In case the e-CRF cannot be accessed and hence the SAE Report Form cannot be filled in within the e-CRF system, a paper SAE Report Form should be used and sent to Ferring Pharmacovigilance using the contact details below.

Ferring Pharmacovigilance

[redacted]

Completion of the Demographics, Adverse Event Log, Medical History Log and Concomitant Medication Log are mandatory for initial reports and for follow-up reports if any relevant changes have been made since the initial report. Data entries must have been made in the e-CRF for Ferring Pharmacovigilance to access the information.

Additional information relevant to the SAE such as hospital records, results from investigations, e.g. laboratory parameters (that are not already uploaded in the e-CRF), invasive procedures, scans and x-rays, and autopsy results can be faxed or scanned and e-mailed to Ferring Pharmacovigilance using the contact details in the section above. In any case this information must be supplied by the investigator upon request from Ferring. On any copies provided, such details such as subject's name, address, and hospital ID number should be concealed and instead subject number should be provided.

The investigator will supply Ferring and the IRB with any additional requested information such as results of post-mortem examinations and hospital records.

Ferring will report all serious adverse events according to local regulations.

8.6 Follow-up of Adverse Events and Serious Adverse Events

8.6.1 Follow-up of Adverse Events with Onset during the Trial

During the trial, the investigator must follow-up on each adverse event until it is resolved or until the medical condition of the subject is stable.

After the subject's last visit, the investigator must follow up on any adverse event classified as serious or considered to have a reasonable possible causality to the IMP until it is resolved or until the medical condition of the subject is stable. All such relevant follow-up information must be reported to Ferring. If the event is a chronic condition, the investigator and Ferring may agree that further follow-up is not required.

8.6.2 Collection of Serious Adverse Events with Onset after Last Visit in the Trial

If an investigator becomes aware of an SAE after the subject's last visit, and he/she assesses the SAE to have a reasonable possible causality to the IMP, the case will have to be reported to Ferring Pharmacovigilance, regardless how long after the end of the trial this takes place.

9 STATISTICAL METHODS

The Global Biometrics Department of Ferring Pharmaceuticals A/S will be responsible for data management, statistical analyses (including the sample size calculation and the statistical analysis plan), production of tables, listings and figures. This section details the planned statistical analysis of the primary endpoints and outlines the planned statistical analysis for the secondary endpoints. All analyses and further description of the statistical methodology for primary as well as secondary endpoints will be included in the statistical analysis plan (SAP). The SAP will be available before breaking the blind.

The Global Health Economics & Outcome Research Department of Ferring Pharmaceuticals A/S will be responsible for the validation of the Women's Endometriosis Diary and the analysis will be described in a separate psychometric analysis plan. The results will be reported separately.

9.1 Determination of Sample Size

The sample size calculation is based on demonstrating superiority of quinagolide vaginal ring compared with placebo vaginal ring on the primary endpoint of the change in mean daily NRS score for endometriosis-related pain at cycle 4. Taking into account of an interim analysis for futility at a conditional power of 5% (see section 9.9) and assuming that the standard deviation of the change in mean daily NRS is 1.5, a sample size of 52 evaluable subjects per group (in total 208 subjects) will have at least 90% power to detect a treatment effect difference of 1.0 unit using a t-test at a 5% two-sided significance level in a pre-defined hierarchical step-down procedure, starting with testing the highest dose versus placebo (see section 9.6.2). Accounting for a 25% drop-out rate as observed in a previous trial,[30] there should be 70 subjects randomized to each treatment group and in total 280 subjects should be randomized. Table 9-1 summarizes the required sample size per group for different assumptions of treatment effect difference and power.

Table 9-1 Sample Size by Treatment Effect Difference

Difference in NRS score reduction between quinagolide vaginal ring the highest dose group and placebo vaginal ring group	Number of subjects per group [a]			
	Evaluable subjects		Randomized subjects [b]	
	Power 80%	Power 90%	Power 80%	Power 90%
0.8	60	80	80	107
0.9	48	64	64	86
1.0	40	52	54	70
1.1	32	44	43	59
1.2	28	36	38	48

a Assuming a standard deviation of 1.5 units and accounting for an interim analysis for futility at a conditional power at current trend of 5%.
b Assuming 25% drop-out rate.

A sample size re-estimation will also be performed at the same time of the interim analysis based on the observed standard deviation and drop-out pattern. The sample size may be increased to 360 subjects in total or 90 subjects per group.

9.2 Subject Disposition

All subjects screened and randomized will be accounted for. Screened subjects who discontinue from the trial prior to randomization are regarded as screening failures. The number of screened but not randomized subjects will be summarized by primary reason for screening failure. The number of subjects re-screened and subjects randomized after re-screening will also be summarized.

Subject disposition with respect to the timing of action during the COVID-19 pandemic will be tabulated using the intention-to-treat (ITT) analysis set. The status of randomized subjects at the time of the temporary trial hold due to the COVID-19 pandemic will be summarized in the following categories: randomized and exited before the hold, randomized before and exited during or after the hold, as well as randomized and exited after the hold.

Subject disposition with respect to analysis set will be tabulated by treatment group for all randomized subjects.

All premature discontinuations will be summarized and listed by time of and reason for discontinuation.

The time to discontinuation will be summarized by the Kaplan-Meier estimates, and the treatment group difference will be tested using the Log-Rank test.

9.3 Protocol Deviations

Major protocol deviations, such as significant non-compliance or other serious unforeseen deviations deemed to invalidate the data and affect the conclusions of the trial, will lead to exclusion of data from the per-protocol (PP) analysis set. Data will not be excluded from the PP analysis set in case of minor protocol deviations. The list of major protocol deviations includes, but is not restricted to:

- Treatment received not in accordance with randomization (only data after the occurrence of the mistake to be deleted)
- Non-compliance with IMP treatment regimen for >20% of days during a non-menstrual period (only data after the first occurrence of non-compliance to be deleted)
- Missing >20% of days of e-Diary recordings during a menstrual cycle (only data of this cycle to be deleted from the respective by-cycle PP analysis)
- Use of prohibited analgesics for >1 day during a menstrual cycle (only data of this cycle to be deleted from the respective by-cycle PP analysis)

The detailed criteria of major protocol deviations will be further defined in the SAP. Unforeseen deviations deemed to impact the primary endpoint of the trial may additionally be rated as major protocol deviations by the Ferring clinical team on the basis of a blinded review of data before declaration of clean-file and lock of database.

The list of major protocol deviations will be detailed and documented in the clean file document prior to database release.

For the subjects who were on treatment at the time of the temporary trial hold due to COVID-19, a listing of selected missing trial assessments will be created. It will include the last trial visit before the hold, expected visits during the hold, missing assessments/visits during the hold and the reasons for missed assessments/visits. A similar listing of ring insertion/removal schedule will also be created for subjects who were on treatment during the hold.

9.4 Analysis Sets

9.4.1 Intention-to-Treat (ITT) Analysis Set

The ITT analysis set comprises all randomized (as planned) subjects.

9.4.2 Per-Protocol (PP) Analysis Set

The PP analysis set is defined as all randomized subjects except those for whom all data are excluded as a result of major protocol deviations as described in section 9.3.

9.4.3 Safety Analysis Set

The safety analysis set comprises all treated subjects and is analyzed according to the actual treatment received.

9.5 Trial Population

9.5.1 Demographics and other Baseline Characteristics

All relevant baseline data will be summarized in tables including the four treatment groups and a total column.

The purpose of these tabulations is to characterize the treatment groups and assess the degree of similarity achieved by the randomization. Baseline data will not be compared using statistical tests. Unless otherwise noted, tabulations will be produced for both the PP and the ITT analysis sets.

Continuous variables will be presented with number of subjects, mean, standard deviation, median, inter-quartile range, minimum, and maximum. Categorical variables will be presented with number and percentage of subjects within each specific category.

9.5.2 Medical History, Concomitant Medication and other Safety Evaluations

Medical history will be coded using MedDRA. The version of MedDRA will be documented. Medical history will be listed by subject and summarized by System Organ Class (SOC) and preferred term.

Prior and concomitant medication will be summarized by ATC classification 1st level (alphabetically), ATC classification 2nd level (in decreasing order of frequency) and treatment group.

Other baseline evaluations including menstrual history, reproductive history, body measurement and vital signs will be presented by descriptive statistics by treatment group.

9.6 Endpoint Assessments

9.6.1 General Considerations

The primary analysis of the primary endpoint will be based on the ITT analysis set, while the analysis of the primary endpoint based on the PP population will be considered supportive and serve as one of the sensitivity analyses.

The analysis of the secondary efficacy endpoints will be performed for both the ITT and PP populations. The safety endpoints will be analyzed for the safety analysis set unless otherwise noted.

Statistical tests will be performed using a two-sided test at a 5% significance level. Treatment differences will (where appropriate) be presented with 95% confidence intervals and p-values corresponding to the statistical test of the hypothesis of "equal effect" against the alternative of "different effect".

The SAP will detail data-handling conventions on cycle and menstrual period definitions.

Continuous variables will be presented with number of subjects, mean, standard deviation, median, inter-quartile range, minimum, and maximum. Categorical variables will be presented with number and percentage of subjects within each specific category.

Missing Data

Missing data for endometriosis-related pain

If a subject has indicated that too much pain is the reason for not completing the diary on some day, the missing data for that day will be derived by taking a worst-case approach, i.e. assigning an NRS of 10 for endometriosis-related pain. Otherwise the score remains to be missing.

As endometriosis-related pain is potentially different during the menstrual-bleedings days from during the non-menstrual-bleeding days, at least 50% of the NRS scores are required to be observed for both the menstrual period and the non-menstrual period to be able to calculate the mean daily NRS score for a particular cycle. As missing NRS scores may not be appropriately balanced across menstrual period and non-menstrual period, the mean daily NRS score based on observed data will be weighted by the lengths of the menstrual period and non-menstrual period to adjust for this potential imbalance.

So the mean daily NRS score is calculated as

$$\frac{l_{mp}\bar{x}_{mp} + l_{non-mp}\bar{x}_{non-mp}}{l_{mp} + l_{non-mp}}$$

Where l_{mp} is the length of the observed menstrual period, l_{non-mp} is the length of the observed non-menstrual period, $\bar{x}_{mp}$ is the mean daily NRS score based on observed NRS scores during the menstrual period, and $\bar{x}_{non-mp}$ is the mean daily NRS score based on observed NRS scores during the non-menstrual period.

The observed cycle length will be based on the first menstrual bleeding date confirmed at the RM+7 visit of each cycle (section 7.4.7). The length of the observed menstrual period will be based on the first and last menstrual bleeding dates confirmed at the RM+7 visit of each cycle. If the last menstrual bleeding date cannot be confirmed at the RM+7 visit (section 7.4.7), the date of the last reported menstrual bleeding day recorded in the e-Diary will be used. The length of the observed non-menstrual period will be calculated as the observed cycle length minus the length of the observed menstrual period.

Missing data for dyspareunia
The mean daily NRS scores for the worst dyspareunia on days with sexual intercourse will be considered missing if the subject reports no sexual intercourse during a cycle. The mean score will be based on non-missing scores and will not be weighted by menstrual period length.

Missing data for adverse events
For adverse events, missing values will be treated as missing, except for causality, intensity, seriousness and outcome of adverse events, where a worst-case approach will be used.

9.6.2 Primary Endpoint

The primary endpoint is the change in the mean daily NRS score for the worst endometriosis-related pain at cycle 4, i.e. the difference between the active treatment group and the placebo group in the change from baseline in the mean daily NRS score for the worst endometriosis-related pain at the end of cycle 4. The baseline is defined as the average of the mean daily NRS scores for endometriosis-related pain of the two run-in cycles (cycles -2 and -1).

The primary endpoint will be analyzed using a repeated measures analysis of covariance (ANCOVA) model, with the change in mean daily NRS score from baseline measured at cycles 1, 2, 3, and 4 as the dependent variable, the baseline mean daily NRS score and the baseline percentage of days on rescue analgesics by type as covariates, as well as the treatment group and treatment by cycle interaction as fixed effect. The error-covariance matrix will be unstructured. The

treatment contrasts between each active treatment versus placebo at cycle 4 will be reported with 95% confidence intervals and corresponding p-values:

$$\begin{cases} H_0^{P1}: & \mu_{QVR,high,4}^{P} = \mu_{Placebo,4}^{P} \\ H_1^{P1}: & \mu_{QVR,high,4}^{P} \neq \mu_{Placebo,4}^{P} \end{cases}$$

$$\begin{cases} H_0^{P2}: & \mu_{QVR,medium,4}^{P} = \mu_{Placebo,4}^{P} \\ H_1^{P2}: & \mu_{QVR,medium,4}^{P} \neq \mu_{Placebo,4}^{P} \end{cases}$$

$$\begin{cases} H_0^{P3}: & \mu_{QVR,low,4}^{P} = \mu_{Placebo,4}^{P} \\ H_1^{P3}: & \mu_{QVR,low,4}^{P} \neq \mu_{Placebo,4}^{P} \end{cases}$$

Where $(H_0^{P1}), (H_0^{P2}), (H_0^{P3})$ are null hypotheses, $(H_1^{P1}), (H_1^{P2}), (H_1^{P3})$ are alternative hypotheses, and

$$\begin{cases} \mu_{QVR,high,4}^{P} = \text{The mean change from baseline in NRS score at cycle 4 for QVR high dose} \\ \mu_{QVR,medium,4}^{P} = \text{The mean change from baseline in NRS score at cycle 4 for QVR medium dose} \\ \mu_{QVR,low,4}^{P} = \text{The mean change from baseline in NRS score at cycle 4 for QVR low dose} \\ \mu_{placebo,4}^{P} = \text{The mean change from baseline in NRS score at cycle 4 for placebo ring} \end{cases}$$

In order to control the overall type I error at 5%, a step-down procedure will be implemented. The testing sequence starts with testing the null hypothesis for the high dose against placebo (H_0^{P1}), and if superiority is established for the high dose $(p^{P1} \leq 0.05)$, the testing will continue by testing the null hypothesis for the medium dose (H_0^{P2}). Again if superiority is established for the medium dose $(p^{P2} \leq 0.05)$, the testing will continue by testing the null hypothesis for the low dose (H_0^{P3}). All the testing will be done at the 5% significance level. If any of the active treatment groups are stopped for safety reasons during the trial, the testing sequence starts with the highest remaining dose.

The primary analysis is based on observed cases (including those missing due to too much endometriosis-related pain) in the ITT population.

Sensitivity Analyses

The following sensitivity analyses will be conducted:

1. To test efficacy in more perfect conditions:
   - The primary analysis in the PP population using observed cases (including those missing due to severe endometriosis-related pain)
2. To test sensitivity to missing data:
   - The ITT analysis without assuming a NRS of 10 on days when subjects were in too much pain to complete the e-Diary

- The ITT analysis based on last-observation-carried-forward (LOCF) method
- The ITT analysis based on baseline-observation-carried-forward (BOCF) method
- The ITT analysis using multiple imputation for missing data in a placebo-based pattern mixture model (based on a missing-not-at-random condition) as described by Ratitch[47]

3. To test for heterogeneity of effect:
   - The ITT analysis testing for treatment by baseline percentage of days on rescue analgesics interaction. This will be done by type of rescue analgesics
   - The ITT analysis testing for treatment by baseline mean daily NRS score interaction
4. The primary analysis using the actual treatment rather than the planned treatment
5. To test the sensitivity to adjustment in the statistical model:
   - The ITT analysis also adjusting for the percentage of days on rescue analgesics by type at cycles 1, 2, 3, and 4 (time dependent)
   - The primary analysis with the baseline defined as the average NRS score for endometriosis-related pain of the last run-in cycle (cycle -1)

Dose-response Model

To assess the dose-response association between the doses of quinagolide and the primary outcome, four dose-response models i.e. a linear dose-response model, an exponential dose-response model, a log linear dose response model, and a sigmoidal dose-response model will be fitted. The best fitting curve will be illustrated together with the dose specific means and standard errors of the mean.

9.6.3 Secondary and Exploratory Endpoints

Secondary endpoints of change from baseline in the mean daily NRS score for the worst dysmenorrhea and for the worst non-menstrual pelvic pain at cycle 4 will be analyzed longitudinally and similarly to the primary endpoint, with the focus on estimating the treatment effect at cycle 4. Sensitivity analyses will not be performed for secondary endpoints.

Secondary endpoints over all 4 cycles or for cycles pre-specified in endpoints will be analyzed longitudinally as follows:

- Continuous endpoints will be analyzed by repeated measures ANCOVA
- Responder status endpoints will be analyzed using repeated measures logistic regression using the generalized estimating equation (GEE) approach for binary data with logit link function and by analyzing the time to event of first response using the proportional odds regression model
- Count data relative to particular cycle days (e.g. number of days of avoiding sexual intercourse relative to the total days of either having sexual intercourse or avoiding it

due to endometriosis-related pain) will be analyzed using repeated measures negative-binomial regression using the GEE approach for count data with log link function using the appropriate off-set

These models will include treatment, cycle and treatment by cycle interaction as independent factors and the respective baseline by cycle interaction (as applicable) and the percentage of days on rescue analgesics by type at baseline as covariates. The error-covariance matrix will be unstructured. The possible dependence of the treatment effect on these covariates will be additionally investigated by testing for respective treatment interactions.

The analysis will focus on adjusted treatment contrasts versus placebo during cycles 1-4. Table 9-2 summarizes the respective analyses for all defined secondary and exploratory endpoints.

Table 9-2 Analyses of Secondary and Exploratory Endpoints

Endpoint	Analysis Method				Cycles
	Repeated measures ANCOVA (focusing on cycle 4)	Repeated measures ANCOVA	Logistic regress-ion (GEE)	Negative Binomial regression (GEE)	
Changes in the mean daily NRS scores for the worst dysmenorrhea and for the worst non-menstrual pelvic pain at cycle 4	X				4
Changes in the mean daily NRS scores for the worst endometriosis-related pain over 4 menstrual cycles		X			1-4
Changes in the mean daily NRS scores for the worst dysmenorrhea and for the worst non-menstrual pelvic pain over 4 menstrual cycles		X			1-4
Changes in the mean daily NRS scores for the worst dyspareunia on days with sexual intercourse over 4 menstrual cycles		X			1-4
Frequency of avoiding sexual intercourse due to expected pain over 4 menstrual cycles				X	1-4
Changes in the mean daily NRS scores for the worst impact of endometriosis-related pain on the subject's ability to function over 4 menstrual cycles		X			1-4
Changes in the mean weekly scores of the EHP-30 pain impact domain over 4 menstrual cycles		X			1-4
Changes in vaginal bleeding pattern over 4 menstrual cycles [a]				X	1-4
Percentage of days with mild and/or strong rescue analgesics used over 4 menstrual cycles				X	1-4
Total and average doses of mild and/or strong rescue analgesics used over 4 menstrual cycles				X	1-4
Responder rate assessed as ≥30%, ≥50% and ≥70% reduction from the baseline in mean daily NRS scores for the worst endometriosis-related pain, dysmenorrhea, non-menstrual pelvic pain and for the worst endometriosis-related pain impact over 4 menstrual cycles			X		1-4[b]
Changes in the mean individual and total symptom and sign severity scores of the B&B scale at cycle 4		X			4[c]
Changes in EHP-30 scores over 4 menstrual cycles		X			1-4
Changes in PGIS scores at cycle 4		X			4[c]
PGIC scores at cycle 4		X			4[c]
Plasma concentration of quinagolide and metabolites during cycles 1 and 4	*Descriptive and population PK modelling*				
Serum levels of mid-luteal phase progesterone at cycle 4 [d]		X			4[c]
Proportion of subjects with serum levels of mid-luteal progesterone ≥25 nmol/L (7.9 ng/mL) at cycle 4 [d]			X		4[c]
Serum levels of mid-luteal estradiol, prolactin, TSH and IGF-1 at cycle 4		X			4[c]
Changes in bone turnover markers, determined by bone resorption marker s-CTx and bone formation marker s-PINP at cycle 4		X			4[c]
Changes in ECG parameters including PR interval, QT interval, QTcF interval and QRS interval at cycle 4	*Descriptive only*				
Proportion of subjects with abnormal clinically significant echocardiography findings indicating valvular heart disease at cycle 4	*Descriptive only*				
Proportion of subjects identified with potential impulse control disorders by the questionnaire for impulsive-compulsive disorders at cycle 4	*Descriptive only*				
Frequency and intensity of adverse events	*Descriptive only*				
Changes in circulating levels of clinical chemistry and hematology parameters, urinalysis parameters, and proportion of subjects with markedly abnormal changes	*Descriptive only*				
Frequency and intensity of ring acceptability and performance parameters over 4 menstrual cycles	*Descriptive only*				
Changes in endometriosis biomarkers such as serum levels of VEGF, PlGF, IL-6 and sFlt-1 at cycle 4 *		X			4[c]

[a] Vaginal bleeding pattern is evaluated as the number of no bleeding, spotting, light bleeding, moderate bleeding and heavy bleeding days, the duration of menstrual and non-menstrual period, and the number of bleeding days during the non-menstrual period.
[b] Responder status is also analyzed by analyzing the time to respective first occurrence of response using the proportional odds regression mode1.
[c] Analysis reduced to cross-sectional analysis when only one cycle is involved.
[d] Only data from visits within the LH+6-9 window will be used.
Note: Safety endpoints highlighted in grey and exploratory endpoint marked with *.

All analyses and respective definitions of the endpoints will be further detailed in the SAP. Plasma concentration of quinagolide and metabolites will be analyzed descriptively. A population PK modelling method will be outlined in a modelling analysis plan under the responsibility of the Translational Medicine Department of Ferring Pharmaceuticals A/S and the results will be reported separately.

For the follow-up cycle (cycle 5), only descriptive summary statistics will be provided as applicable.

9.7 Extent of Exposure and Treatment Compliance

The extent of exposure is defined as the number of days between the first ring insertion until removal and will be summarized by cycle and treatment group. The total extent of exposure (across all cycles) will be summarized by treatment group and overall. This will be done both including and excluding known periods of intermittent removals of the vaginal ring if applicable.

The number of days of rescue analgesics use and the percentage of days on rescue analgesics will be similarly summarized.

9.8 Safety Endpoints

General Considerations

This section describes the descriptive analyses of safety endpoints and routine safety assessments. The safety endpoints, highlighted in grey in Table 9-2, will be analyzed for the safety analysis set.

Changes in Bone-turnover Markers

Changes in bone-turnover markers will be analyzed by an ANCOVA model, estimating adjusted treatment contrasts at cycle 4, as described in Table 9-2 in section 9.6.3.

ECG and Echocardiography

Changes in ECG parameters, including PR interval, QT interval, QTcF interval and QRS interval at cycle 4 will be summarized by cycle and treatment group and in total.

The proportion of subjects with clinically significant echocardiography findings will be tabulated by cycle and treatment group and in total.

Questionnaire for Impulsive-Compulsive Disorders

Frequency-tables for each item of the questionnaire for impulsive-compulsive disorders as well as the proportion of subjects having potential behaviors associated with impulse control disorders will be presented by cycle, treatment and in total.

Adverse Events

Treatment-emergent adverse events[g] will be summarized overall and tabulated by SOC and preferred term using MedDRA. The version of MedDRA will be documented. The total number of subjects reporting an adverse event, the percentage of subjects (%) with an adverse event, and the number of events reported will be presented.

Summary tables will be prepared for the following: all adverse events, adverse events by causality (reasonable possibility / no reasonable possibility), adverse events leading to death, adverse events by intensity (mild / moderate/ severe), adverse reactions by intensity (mild / moderate/ severe), SAEs, adverse events leading to discontinuation, adverse events with an incidence of at least 5% in any treatment group, non-SAEs with an incidence of at least 5% in any treatment group. A separate data listing will be provided for pre-treatment adverse events.[h] Listings of adverse events will also indicate whether or not the adverse event occurs during the COVID-19 trial hold.

Safety Laboratory Variables

Safety laboratory variables will be grouped under “hematology” and “clinical chemistry”.

The baseline is taken on LH+7 of cycle -1. Post-baseline clinical laboratory values are taken on LH+7 of cycle 4.

The circulating levels of clinical chemistry and hematology parameters including changes from baseline will be tabulated for each time point for each laboratory variable.

Shift tables will be prepared to compare baseline values to the values at the respective post-baseline visits, using a categorization of low, normal and high values defined according to the reference ranges provided by the central laboratory.

For each laboratory variable, a summary table will be prepared displaying the proportion of subjects who have at least one post baseline markedly abnormal value. The denominator will be the number of subjects with baseline and at least one post baseline value. The table will also include a break-down by classification of the baseline value. Markedly abnormal criteria for the safety laboratory values will be specified in the SAP.

All laboratory values will be listed by subject number and time point. Values outside the reference range and markedly abnormal values will be flagged.

Urinalysis

Urinalysis parameters will be summarized descriptively.

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[g] A treatment-emergent adverse event is any adverse event occurring after start of IMP and before the end-of-trial visit, or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after start of IMP and before the end-of-trial visit.

[h] A pre-treatment adverse event is any adverse event occurring after signed informed consent and before start of IMP or a pre-existing condition that worsens in intensity after signed informed consent but before start of IMP.

Ring Acceptability Parameters

Frequency-tables for each item (as applicable) of the ring acceptability questionnaire will be presented by cycle, treatment group and in total.

Other Safety Variables

Vital Signs

Vital signs and the changes in vital signs will be analyzed similarly to routine safety laboratory variables. Reference ranges for vital signs will be specified in the SAP.

Physical and Gynecological Examination

Physical and gynecological examination findings at end-of-treatment compared to screening will be summarized in shift tables and all subjects with any abnormal finding will be listed by subject and time point. The list will include both screening and end-of-treatment assessment for comparison.

Transvaginal Ultrasound

Endometrial thickness, number and size of fibroids if presented and number and size of ovarian cyst if presented will be tabulated by screening, RM+7 visits of cycle 4.

9.9 Interim Analysis

An interim analysis with the option to stop the trial early due to futility will be performed by an external statistician, when approximately half of the planned evaluable subjects (104 subjects) have completed the treatment period of the trial for the assessment of the primary endpoint, using unblinded data presented by treatment group.

The futility bound is set at a conditional power using current trend equal to 5%, which means that the trial could potentially be stopped for futility, if the probability of achieving a significant result in the highest remaining dose group is lower than 5% based on the observed data at the interim analysis. In case of high drop-out rate or discontinuations in the highest dose group, the analysis will be performed on the remaining dose(s). If the probability is between 5% and 90%, the sample size will be re-estimated by the external statistician based on the unblinded data available at the interim analysis and may be increased to a total of 360 subjects.

No interim analysis intended to stop the trial early due to overwhelming efficacy is planned.

10 DATA HANDLING

10.1 Source Data and Source Documents

Source Data – ICH Definition

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents – ICH Definition

Source documents are defined as original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Trial-specific Source Data Requirements – Ferring

Source documents need to be preserved for the maximum period of time permitted by local requirements. For each subject screened, the investigator will indicate as a minimum in the source documents that informed consent is obtained, whether wash-out is needed, the date and the reason for wash-out if applicable and the reason for screening failure if applicable. For each subject randomized, the investigator will indicate in the source documents that the subject participates in this trial, and will record at least the following information, if applicable:

- Existence of subject (initials, date of birth)
- Confirmation of participation in trial (trial ID, subject ID)
- Informed consent(s) (date of obtaining written informed consent(s))
- Eligibility for participation in the trial (documenting all inclusion / exclusion criteria)
- Relevant medical history and menstrual history
- Visit dates
- Dates of insertion/removal of the ring
- Dispensing of IMP and ibuprofen
- Dates and doses of concomitant medications
- Adverse events (description as well as start/stop date and time)
- Reason for discontinuation
- Event of unblinding, including the reason for unblinding

The source data for analytical parameters of blood samples will be available at the central laboratory.

In addition, each subject will use an e-Diary on a daily basis to record the following specific protocol data, for which the e-PRO service provider database is considered source data:

- Assessment of endometriosis-related pain on NRS scale
- Vaginal bleeding
- Occurrence of sexual intercourse and assessment of dyspareunia (if applicable)
- Pain impact (also applicable to the weekly pain impact questions)
- Analgesic use

Note that part of the analgesic use information, such as prescriptions of hydrocodone-acetaminophen or information of other analgesics, will be recorded in the e-CRF.

At a few selected visits, subjects, study coordinators and investigators will access electronic tablets separately to record the following data, for which the e-PRO service provider database is considered source data:

- B&B scores
- EHP-30 scores
- PGIS and PGIC scores
- QICD scores
- Ring acceptability

For the eC-SSRS, the e-PRO service database is also considered source data. The text files of transcripts will be considered source documents for patient interviews.

10.2 e-CRF

An e-CRF system provided by an independent third-party CRO, Target Health Inc., will be used for data capture. The system is validated and access at all levels to the system is granted / revoked following Ferring and vendor procedures, in accordance with regulatory and system requirements.

Trial data should be entered into the e-CRF within a reasonable time after the subject has attended a visit or after the data become available, as applicable.

The investigator will approve / authorize the e-CRF entries for each subject with an electronic signature which is equivalent to a handwritten signature.

The e-CRF system and the database will be hosted at Target Health Inc. After the trial database is declared clean and is released to the responsible statistician, a final copy of the database will be stored at Ferring. The investigator will also receive a copy of the trial site's final and locked data (including audit trail, electronic signature and queries) as write-protected PDF-files produced by Target Health Inc. The PDF-files will be stored in an electronic format and will be provided to the investigator before access to the e-CRF is revoked.

Entry errors occurring in the e-CRF will be corrected electronically. Such corrections or modifications will be automatically tracked by an audit trail detailing the date and time of the correction and the name of the person making the correction.

10.3 Use of Patient Reported Outcome

A newly developed PRO tool, Women's Endometriosis Diary, which consists of questions on endometriosis-related pain, vaginal bleeding, occurrence of sexual intercourse and the impact of endometriosis-related pain on functioning, is to be used in the present trial. Questions on daily analgesic use are included in the daily e-Diary, although they are not part of Women's Endometriosis Diary. The development of the PRO is consistent with the FDA's PRO guidance[33] and follows the patient-focused outcome measurement road map.

All diary questions are administered electronically through an application-based technology (app) on a hand-held device in the form of either the subject's own phone or a provisional device.

The e-Diary data will be encrypted to ensure personal data privacy. No personal data will be collected by Ferring from the subjects' own phones, if subjects choose to use their own phones. The download and installation process of the app will be controlled through a subject-specific activation code, allowing only subjects participating in the trial to download and install the app. The app will be PIN-protected to ensure that only the individual subject will be able to access the app.

The electronic data collection procedure is compliant with FDA 21 CFR part 11 for electronic records. Once subjects have submitted their recordings, the data will be transmitted from subjects' own phones or from their provisional devices to a third party database with backup and cyber-security controls. No access to historically reported data will be given to the subjects once they have submitted their recordings. Furthermore, no retrospective data entry will be allowed, i.e. no data entry after closure of the entry window, which is from 8 pm to 2 am every day for the daily diary and from 8 pm on Sundays to 2 am on Tuesdays for the weekly diary. Reminders will be set up to remind subjects of completing the diary when applicable. In the present trial, the investigator or the trial coordinator will be encouraged to review the e-Diary data regularly in order to monitor subject compliance with the e-Diary completion and analgesic use. No modification of subject reported e-Diary data will be made.

In addition to the PRO collected via e-Diary, B&B, EHP-30, PGIS, PGIC, questionnaire for impulsive-compulsive disorders and ring acceptability questionnaire will be completed at the site via electronic tablets.

10.4 Data Management

A data management plan will be created under the responsibility of the Global Biometrics Department of Ferring. The data management plan will be issued before data collection begins and will describe all functions, processes, and specifications for data collection and validation. The data

management plan will also include information about the intended use of computerized systems, a description of the security measures employed to protect the data and a description of the electronic data flow.

10.5 Provision of Additional Information

On request, the investigator will provide Ferring with additional data relating to the trial, duly anonymized and protected in accordance with applicable requirements.

11 MONITORING PROCEDURES

11.1 Periodic Monitoring

The monitor will contact and visit the investigator periodically to ensure adherence to the protocol, International Conference on Harmonisation-Good Clinical Practice (ICH-GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy and verifiability of e-CRF entries compared to source data, verification of drug accountability and compliance to safety reporting instructions.

The investigator will permit the monitor direct access to all source data, including e-diaries, electronic medical records, and/or documents in order to facilitate data verification. The investigator will cooperate with the monitor to ensure that any discrepancies that may be identified are resolved. The investigator is expected to be able to meet the monitor during these visits. Shortly after a subject is screened and determined eligible, a monitoring visit will take place. For this trial, the frequency of the monitoring visits per site will be dependent on recruitment rate, observed data quality and overall site performance.

The source data verification process, definition of key variables to be monitored and the monitoring strategy will be described in detail in the Monitoring Plan for the trial.

11.2 Audit and Inspection

The investigator will make all the trial-related source data and records available at any time to quality assurance auditor(s) mandated by Ferring, or to domestic / foreign regulatory inspectors or representatives from IRBs who may audit / inspect the trial.

The main purposes of an audit or inspection are to evaluate trial conduct and compliance with the trial protocol, ICH-GCP, the applicable regulatory requirements and standard operating procedures.

The subjects must be informed by the investigator and in the Informed Consent Documents that authorized Ferring representatives and representatives from relevant regulatory authorities and IRBs may wish to inspect their medical records. During audits / inspections the auditors / inspectors may copy relevant parts of the medical records. No personal identification apart from the screening / randomization number will appear on these copies.

The investigator should notify Ferring without any delay of any inspection by regulatory authorities or IRBs.

11.3 Confidentiality of Subject Data

The investigator will ensure that the confidentiality of the subjects' data will be preserved. In the e-CRF or any other documents submitted to Ferring, the subjects will not be identified by their names, but by an identification system, which consists of an assigned number in the trial.

Documents that are not for submission to Ferring, e.g. the confidential subject identification code and the signed Informed Consent Documents, will be maintained by the investigator in strict confidence.

12 CHANGES IN THE CONDUCT OF THE TRIAL

12.1 Protocol Amendments

Any change to this protocol will be documented in a protocol amendment, issued by Ferring, and agreed upon by the investigator and Ferring prior to its implementation. Amendments may be submitted for consideration to the approving IRBs and regulatory authorities in accordance with local regulations. Changes to the protocol to eliminate immediate hazard(s) to trial subjects may be implemented prior to IRBs' approval or favorable opinion.

12.2 Deviations from the Protocol

Deviations from the protocol should not occur. If deviations occur, the investigator must inform the sponsor, and a record of protocol deviations will be maintained by the investigator and sponsor.

12.3 Premature Trial Termination

Both the investigator (with regard to his/her participation) and Ferring reserve the right to terminate the trial at any time. Should this become necessary, the procedures will be agreed upon after consultation between the two parties. In terminating the trial, Ferring and the investigator will ensure that adequate consideration is given to the protection of the best interests of the subjects. Regulatory authorities and IRBs will be informed.

In addition, Ferring reserves the right to terminate the participation of individual trial sites. Conditions that may warrant termination include, but are not limited to, insufficient adherence to protocol requirements and failure to enter subjects at an acceptable rate.

13 REPORTING AND PUBLICATION

13.1 Clinical Trial Report

The data and information collected during this trial will be reported in a clinical trial report prepared by Ferring and submitted for comments and signature to the signatory investigator.

13.2 Confidentiality and Ownership of Trial Data

Any confidential information relating to the IMP or the trial, including any data and results from the trial will be the exclusive property of Ferring. The investigator and any other persons involved in the trial will protect the confidentiality of this proprietary information belonging to Ferring.

13.3 Publications and Public Disclosure

13.3.1 Publication Policy

At the end of the trial, one or more manuscripts for joint publication may be prepared in collaboration between the investigator(s) offered authorship and Ferring. In a multi-site trial based on the collaboration of many sites, any publication of results must acknowledge all sites. Results from multi-site trials must be reported in entirety in a responsible and coherent manner and results from subsets should not be published in advance or without clear reference to the primary publication of the entire trial.

Authorship is granted based on the criteria established by the International Committee of Medical Journal Editors (ICMJE) (see current official version http/www.ICMJE.org).[48] The total number of authors is based on the guideline from the relevant journal or congress. In the event of any disagreement in the content of a publication, both the investigator's and Ferring's opinion will be fairly and sufficiently represented in the publication.

Any external CRO or laboratory involved in the conduct of this trial has no publication rights regarding this trial.

If the investigator wishes to independently publish / present any results from the trial, the draft manuscript / presentation must be submitted in writing to Ferring for comments prior to submission. Comments will be given within four weeks from receipt of the draft manuscript. This statement does not give Ferring any editorial rights over the content of a publication, other than to restrict the disclosure of Ferring's intellectual property. If the matter considered for publication is deemed patentable by Ferring, scientific publication will not be allowed until after a filed patent application is published. Under such conditions the publication will be modified or delayed at the investigator's discretion, to allow sufficient time for Ferring to seek patent protection of the invention.

13.3.2 Public Disclosure Policy

ICMJE member journals have adopted a trial-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public, clinical trials registry. Thus, it is the responsibility of Ferring to register the trial in an appropriate public registry, i.e. www.ClinicalTrials.gov; a website maintained by the National Library of Medicine at National Institutes of Health in the United States. A summary of the trial results is made publicly available in accordance with applicable regulatory requirements.

14 ETHICAL AND REGULATORY ASPECTS

14.1 Institutional Review Board

An IRB will review the protocol and any amendments and advertisements used for recruitment. The IRB will review the Subject Information Sheet and the Informed Consent Form, their updates (if any), and any written materials given to the subjects. A list of all IRBs to which the protocol has been submitted and the name of the committee chairmen will be included in the Clinical Trial Report.

14.2 Regulatory Authorities' Approval

The regulatory permission to perform the trial will be obtained in accordance with applicable regulatory requirements. All ethical and regulatory approvals must be available before a subject is exposed to any trial-related procedure, including screening tests for eligibility.

14.3 End-of-Trial

The end of the trial is defined as the date of LPLV, i.e. when the last subject completes the end-of-trial visit. The IRBs will be notified about the completion of the clinical trial according to local legislation.

In the case of early termination for safety reasons, Ferring must notify the end of the trial to the relevant regulatory authorities and the concerned IRBs without delay, clearly explain the reasons, and describe follow-up measures, if any.

14.4 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, in compliance with the approved protocol, ICH-GCP and applicable regulatory requirements.

14.5 Subject Information and Consent

This trial will use three sets of Informed Consent Documents: one overall covering the trial participation, one specific covering the genetic testing for analysis of pharmacogenetics and for potential analyses of cell-free DNA and microRNA as well as one specific covering the patient interview. The latter two documents will only describe the aspects relevant to the genetic analysis or to the patient interview and should be read in conjunction with the Informed Consent Document for the general trial. Participation in the genetic testing and participation in the patient interview are both optional.

The investigator (or the person delegated by the investigator) will obtain a freely given written consent from each subject after an appropriate explanation of the aims, methods, sources of

funding, any possible conflicts of interest, anticipated benefits, potential hazards, and any other aspects of the trial which are relevant to the subject's decision to participate. The trial subject must be given ample time to consider participation in the trial, before the consent is obtained. The Informed Consent Documents must be signed and dated by the subject and the investigator who has provided information to the subject regarding the trial before the subject is exposed to any trial-related procedure, including screening tests for eligibility. Subjects must be given the option of being informed about the general outcome and the results of the trial.

The investigator (or the person delegated by the investigator) will explain that the subject is completely free to refuse to enter the trial or to withdraw from it at any time, without any consequences for her further care and without the need to justify her decision.

The subject will receive a copy of the Subject Information and her signed Informed Consent Form(s) before any trial-related procedures.

If new information becomes available that may be relevant to the trial subject's willingness to continue participation in the trial, a new Subject Information and Informed Consent Form will be forwarded to the IRBs (and regulatory authorities, if required). The trial subjects will be informed about this new information and re-consent will be obtained.

Each subject will be informed that the monitor(s), quality assurance auditor(s) mandated by Ferring, IRB representatives or regulatory authorities' inspector(s), in accordance with applicable regulatory requirements, may review her source records and data. Data protection will be handled in compliance with regulations of the United States.

14.6 Subject Participation Card

The subject will be provided with a Subject Participation Card with the following information:

- That she is participating in a clinical trial
- That she is treated with quinagolide (a dopamine agonist) vaginal ring or placebo vaginal ring for endometriosis-related pain
- The name and phone number of the investigator
- The name and address of Ferring (if required by local regulations)

The subject will be asked to keep the Subject Participation Card in her possession at all times during the trial.

Additionally, each subject's primary care physician will be notified of their participation in the trial by the investigator, if the subject agrees and if applicable.

14.7 Compliance Reference Documents

The Declaration of Helsinki, the consolidated ICH-GCP, and other national law(s) in the United States where the trial takes place shall constitute the main reference guidelines for ethical and regulatory conduct.

15 LIABILITIES AND INSURANCE

15.1 ICH-GCP Responsibilities

The responsibilities of Ferring, the monitor and the investigator are defined in the ICH-GCP consolidated guideline, and applicable regulatory requirements in the United States where the trial takes place. The investigator is responsible for adhering to the ICH-GCP responsibilities of investigators, for dispensing the IMP in accordance with the approved protocol or an approved amendment, and for its secure storage and safe handling throughout the trial.

15.2 Liabilities and Insurance

Ferring is, as sponsor, responsible for ensuring appropriate general/product liability insurance and, as required in accordance with applicable laws and regulations, country-specific liability insurance coverage for claims made by a trial subject for injury arising from the subject's participation in the trial.

16 ARCHIVING

16.1 Investigator File

The investigator is responsible for maintaining all the records, which enable the conduct of the trial at the site to be fully understood, in compliance with ICH-GCP. The trial documentation including all the relevant correspondence should be kept by the investigator for at least 15 years after the completion or discontinuation of the trial, if no further instructions are given by Ferring.

The investigator is responsible for the completion and maintenance of the confidential subject identification code which provides the sole link between named subject source records and anonymous e-CRF data for Ferring. The investigator must arrange for the retention of this Subject Identification Log and signed Informed Consent Documents for at least 15 years after the completion or discontinuation of the trial.

No trial site document may be destroyed without prior written agreement between the investigator and Ferring. Should the investigator elect to assign the trial documents to another party, or move them to another location, Ferring must be notified. If the investigator retires and the documents can no longer be archived by the site, Ferring can arrange having the Investigator File archived at an external archive.

16.2 Trial Master File

Ferring will archive the Trial Master File in accordance with ICH-GCP and applicable regulatory requirements.

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