Cover Page for Statistical Analysis Plan

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	31 May 2022

STATISTICAL ANALYSIS PLAN

RAQUEL
Randomized Trial Assessing Quinagolide Vaginal Ring for Endometriosis-Related Pain
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 8 menstrual cycles in women with moderate to severe endometriosis-related pain

Trial 000165

Investigational Medicinal Product: FE 999051, Quinagolide Vaginal Ring

Indication: Endometriosis-related pain

Phase: 2

Author: [redacted]

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1 Introduction

This document describes the planned statistical analyses for trial 000165, and is based on versions 4.0, 5.0, and 6.0 of the clinical trial protocol dated 9th of July 2018, 27th of March 2019, and 29th of May 2020.

During this trial subjects were randomized under three consecutive versions of the protocol; version 4.0, version 5.0, and version 6.0. As the majority of subjects were randomized under protocol version 5.0, this will be used as the basis for the clinical trial report.

These protocol amendments included modifications to the eligibility criteria, modifications to the overall trial design, and changes to reflect the impact of the COVID-19 pandemic on the conduct of the trial. The change in trial design was in protocol version 6.0, the quinagolide extended-release vaginal rings were administered sequentially for 4 menstrual cycles instead of 8 menstrual cycles. Therefore, in version 6 subjects completed treatment Part A (cycles 1 to 4) only, there was no treatment Part B (cycles 5 to 8), and the follow-up period was for one menstrual cycle only (cycle 5).

The trial was terminated early. The decision was taken due to the results from the parallel phase 2 trial in Europe (Trial 000295) and the continued difficulties with subject recruitment.

Furthermore, due to the low number of subjects recruited, no interim analysis will be performed, and no statistical analysis will be performed. Instead results are presented as descriptive statistics by treatment group separately for Part A and Part B. In this SAP when results are summarized by treatment it means two tables one for Part A (with 4 treatments, Placebo and the 3 doses of quinagolide) and one for Part B (with 6 treatments, Placebo followed by each of the 3 doses of Quinagolide and continued use of each of the 3 doses of quinagolide).

1.1 Definitions/ Abbreviations

1.1.1 Definition of Terms

Terms	Definitions
Randomized	Subject randomized to trial treatment
Screened	Subject who enters the screening phase

1.1.2 Abbreviations

Abbreviations	Meaning of abbreviations in document
ITT	Intention-to-treat
PP	Per-Protocol
IMP	Investigational Medicinal Product
ECG	Electrocardiography
NRS	Numerical Rating Scale
EHP-30	Endometriosis Health Profile-30
B&B	Biberoglu and Behrman
PGIS	Patient Global Impression of Severity
PGIC	Patient Global Impression of Change
e-Diary	Electronic diary
LH	Luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
RM	Return of menses
ANCOVA	Analysis of covariance
GEE	Generalized estimating equation
AE	Adverse event
TEAE	Treatment emergent adverse event
SOC	System organ class
PT	Preferred term

2 Trial Objectives and Endpoints

2.1 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

2.2 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 tool: Women's Endometriosis Diary, The reporting of this objective will not be covered by this SAP as it will be reported separately.

2.3 Exploratory Objective

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

2.4 Primary Endpoint

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

2.5 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 8 menstrual cycles

- Changes in the mean daily NRS scores for the worst dysmenorrhea over 8 menstrual cycles
- Changes in the mean daily NRS scores for the worst non-menstrual pelvic pain over 8 menstrual cycles
- Changes in the mean daily NRS scores for the worst dyspareunia on days with sexual intercourse over 8 menstrual cycles
- Frequency of avoiding sexual intercourse due to expected pain over 8 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 8 menstrual cycles
- Changes in the mean weekly scores of the Endometriosis Health Profile-30 (EHP-30) pain impact domain over 8 menstrual cycles
- Changes in vaginal bleeding pattern over 8 menstrual cycles
- Percentage of days with mild and/or strong rescue analgesics used over 8 menstrual cycles
- Total and average doses of mild and/or strong rescue analgesics used over 8 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 8 menstrual cycles
- Changes in the mean individual and total symptom and sign severity scores of the Biberoglu and Behrman (B&B) scale at cycles 4 and 8
- Changes in the EHP-30 scores over 8 menstrual cycles
- Changes in Patient Global Impression of Severity (PGIS) scores at cycles 4 and 8
- Patient Global Impression of Change (PGIC) scores at cycles 4 and 8
- Plasma concentration of quinagolide and metabolites during cycles 1, 4 and 8
- Serum levels of mid-luteal phase progesterone at cycles 1, 4 and 8
- Proportion of subjects with serum levels of mid-luteal progesterone ≥25 nmol/L (7.9 ng/mL) at cycles 1, 4 and 8
- Serum levels of mid-luteal estradiol, prolactin, thyroid-stimulating hormone (TSH) and insulin-like growth factor-1 (IGF-1) at cycles 1, 4 and 8
- 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 cycles 4 and 8
- Changes in ECG parameters including PR interval, QT interval, corrected QT using Fridericia's formula (QTcF) and QRS interval at cycles 4 and 8
- Proportion of subjects with abnormal clinically significant echocardiography findings indicating valvular heart disease at cycles 4 and 8
- Proportion of subjects identified with potential impulse control disorders by the questionnaire for impulsive-compulsive disorders at cycles 4 and 8
- 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 8 menstrual cycles

2.6 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 cycles 4 and 8.

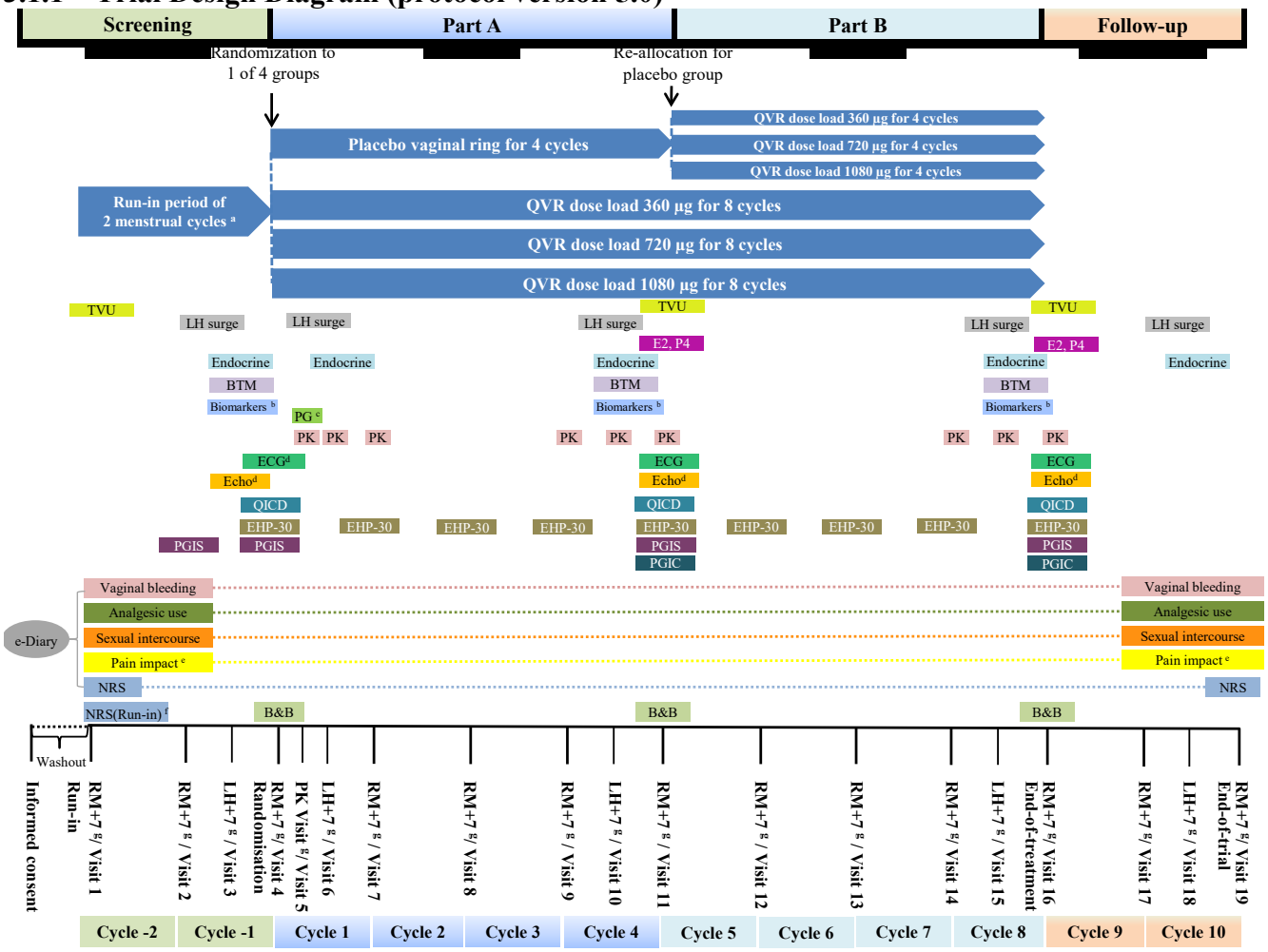
3 Trial design

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) Part A: 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) Part B: double-blind, extension treatment with three doses of quinagolide extended-release vaginal ring administered sequentially for four menstrual cycles (cycles 5, 6, 7 and 8)
4) Follow-up: post-treatment follow-up period of two menstrual cycles (cycles 9 and 10)

3.1.1 Trial Design Diagram (protocol version 5.0)



Abbreviations: B&B=Biberoglu and Behrman Scale, BTM=bone turnover markers, E2=estradiol, 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, P4=progesterone, 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, 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 e-Diary recording for cycle -2.
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. Echo at cycles 4 and 8 can be performed within ±2 weeks of visits 11 and 16, respectively.
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).

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.

At the run-in visit, 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 (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.).

Part A: Subjects will be randomized into Part A of the trial 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).

Part B: Subjects who have received active treatment in Part A will continue with the same doses in Part B, and those who have received placebo vaginal ring in Part A will be re-allocated in a pre-determined 1:1:1 ratio to quinagolide vaginal ring dose load 360 µg, 720 µg or 1080 µg at a target release rate of quinagolide 4.5 µg/day, 9 µg/day or 13.5 µg/day, respectively, administered for four menstrual cycles in Part B (cycles 5, 6, 7 and 8).

Follow-up: Subjects who complete both Part A and Part B will be followed up for two menstrual cycles (cycles 9 and 10).

From randomization to follow-up (cycle 1 to cycle 10), 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 (Part A and Part B), subjects will self-insert the assigned ring in the upper part of the vagina on RM+7 of cycle 1 to cycle 8 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, at cycles 4 and 8, 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 8. PGIS scale will be completed electronically by subjects at cycle -2, at randomization and at cycles 4 and 8, while PGIC scale will be completed electronically at cycles 4 and 8.

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. A full endocrine panel including estradiol, progesterone, prolactin, TSH and IGF-1 will be assessed at the mid-luteal phase of cycles -1, 1, 4, 8 and 10. Evidence of ovulation will be evaluated by serum levels of mid-luteal progesterone. A partial endocrine panel consisting of estradiol and progesterone only will also be assessed at RM+7 visits of cycles 4 and 8. 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, 4 and 8. Blood samples for endometriosis biomarkers including, but not limited to, VEGF, PlGF, IL-6 and sFlt-1 will be collected during cycles -1, 4, and 8. 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 cycles -1, 4, 8 and 10. Quinagolide and metabolites will be measured within 1-5 days of first ring insertion, at both LH+7 visits and RM+7 visits of cycles 1, 4 and 8 as well as at RM+7 visits of cycles 3 and 7. 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.

ECG and echocardiography will be performed to monitor cardiovascular safety. ECG will be assessed prior to randomization during cycle -1, at cycles 4 and 8 (prior to or at visit 4, at visits 11 and 16). ECG must be performed after vital signs but before blood sampling as applicable. ECG and echocardiography at screening can be arranged anytime during cycle -1, e.g. at LH+7 visit but results must be available prior to randomization.

Echocardiography at cycles 4 and 8 can be performed within ±2 weeks of end-of-cycle 4 visit and end-of-cycle 8 visit, respectively.

A modified questionnaire for impulsive-compulsive disorders will be completed electronically by trained trial coordinators based on subjects' verbal response prior to randomization at cycle -1, at cycles 4 and 8.

A urine pregnancy test will be performed at each clinic visit (except for the PK visit during cycle 1) 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 at the run-in visit, at cycles 4 and 8.

The self-assessments of NRS, occurrence of sexual intercourse, the impact of pain, vaginal bleeding and analgesics use will be done by the subjects in the e-Diary. The daily e-Diary should be completed by the subjects before bedtime every night throughout the trial that is from visit 1 until the end-of-trial visit. Additional assessments of pain impact will be done in the weekly e-Diary. The weekly e-Diary should be completed at the end of each week throughout the trial that is from visit 1 to end-of-trial visit.

3.2 General Design Considerations

3.3 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 11) 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. Accounting for a 25% drop-out rate as observed in a previous trial there should be 70 subjects randomized to each treatment group and in total 280 subjects should be randomized. Table 3-1 summarizes the required sample size per group for different assumptions of treatment effect difference and power.

Table 3-1 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 was planned to be performed at the same time of the interim analysis based on the observed standard deviation and drop-out pattern. The sample size could have been increased to 360 subjects in total or 90 subjects per group.

4 Subject Disposition

For the reporting of subject disposition with regard to the Per-Protocol (PP) analysis set the definition of being excluded from the PP population is if the subjects cycle 4 data is exclude from the PP analysis set.

4.1 Screened subjects

Screened subjects who discontinue prior to randomization are regarded as screening failures. All subjects screened will be accounted for (in total and by trial site). The total number of screened subjects will be summarized (n and % of total number of screened subjects) by: randomized, reason for failure (inclusion /exclusion not met, withdrawal by subject, other) and all.

4.2 Subject disposition

Subject disposition with respect to analysis sets (Safety, ITT, and PP) will be summarized by treatment.

4.3 Subject disposition and completion

Subject disposition with respect to analysis sets (Safety, ITT, and PP) and completion of treatment and follow-up will be summarized. Completion of treatment will be based on the end of treatment form and the timing of the potential discontinuation (is end-of cycle 4 visit performed or not), and completion of follow-up will be based on the end of trial form.

4.4 Subject completion/discontinuation

Completion of treatment, and follow-up will be defined as in the subsection 4.3.

Based on the ITT analysis set subjects completion by end of treatment and follow up, will be summarised: completed, discontinued (primary reason for discontinuation according to end of treatment form), by treatment.

4.5 Listing

The subjects screened but not randomized/allocated to treatment will be presented with the reason(s) for screen failure in a data listing.

Based on the ITT analysis set subject disposition with respect to analysis sets will be listed sorted by site, treatment and subject. Subjects who discontinued from the trial will be listed sorted by site, treatment, and subject including information on timing of and reason for discontinuation.

5 Protocol Deviations

Protocol deviations will be rated as either minor or major. Protocol deviations impacting the primary endpoint and thereby affecting the conclusions of the trial will in this SAP be rated as major. Major protocol deviations will lead to exclusion of data from the PP analysis set. Data will not be excluded from the data analysis 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)

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.

5.1 Major protocol deviations

Based on the ITT analysis set major protocol violations will be summarized (n and %) for each category of protocol violation, by treatment and in total.

5.2 Listing

Based on the ITT analysis set subjects with minor or major protocol deviations will be listed and the list will be sorted by site, treatment and subject number. The listing will include category and description of protocol deviation.

6 Analysis Sets

6.1 Intention-To-Treat Analysis Set

The intention-to-treat (ITT) analysis set comprises of all randomized subjects. Treatment assignment for summaries and analyses are according to planned treatment.

6.2 Per Protocol Analysis Set

The PP analysis set is defined as all data from the ITT analysis set except data excluded due to major protocol deviations as defined in section 5. As defined in section 5 some protocol violations will lead to exclusion of parts of a subject's data, not the entire subject.

6.3 Safety Analysis Set

The safety analysis set comprises all treated subjects and are analysed according to the actual treatment received. If more than one treatment is received the highest dose of Quinagolide will be used.

7 Trial Population

Unless otherwise specified all tables and listing in this section will be based on the ITT analysis set.

All summaries in this section will be presented by treatments and a total column

Categorical data will be summarised using numbers and percentages in addition to the sum 'all'. The percentages are based on the total number of subjects with a corresponding assessment. Continuous data will be presented, using the number of subjects (n), mean and standard deviation, median, 25th percentile, 75th percentile, minimum and maximum.

7.1 Demographics and Other Baseline Characteristics

7.1.1 Demographics and body measurements

Baseline demographics variables (age, race and ethnic origin, height, weight and BMI) will be summarized.

7.1.2 Vital Signs at Baseline

Baseline (visit 4) vital signs will be summarised as described in section 10.4.1.

7.1.3 History of Disease

The worst endometriosis-related pain on the NRS based on a recall of experience in the past menstrual cycle will be summarized as a categorical variable.

Endometriosis initial diagnosis (time since initial diagnosis, method, stage and documentation of histology of biopsy) will be summarised.

Endometriosis surgical history (Any history (yes/no), time since, method and type of surgery) will be summarised.

Menstrual history and reproductive history will be summarised.

7.2 Medical History

Medical history recorded at screening visit will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0.

Medical history will be summarised by system organ class (SOC) sorted alphabetically and preferred term (PT) sorted in decreasing frequency of occurrence.

Ongoing and past medical history will be reported separately and the number of subjects with any ongoing or past medical history will be included.

7.3 Prior and Concomitant Medication

Prior and concomitant medication will be summarised by ATC classification 1st level (alphabetically), ATC classification 2nd level (in decreasing order of frequency) and treatment group. These medications will be tabulated separately for:

1) Prior medication; i.e. medication taken exclusively prior to treatment (i.e. with stop date before date of first ring insertion);
2) Concomitant medication, i.e. medication taken during the treatment period (i.e. medication that was not stopped before date of first ring insertion and not started after the last ring removal.
3) Post-treatment medications, i.e. medications starting after the treatment period (i.e. with start after the last IMP removal).

The number of subjects with "any medication" will be included in these tables. If the timing of the dose of a concomitant medication cannot be established in relation to the administration of IMP, it will be considered as concomitant medication.

7.4 Physical Examination

Subjects with abnormalities at any screening, or post-baseline visit will be listed with all physical examination evaluations.

7.5 Listings

Baseline characteristic not listed elsewhere will be listed sorted by site treatment and subject number.

Medical history will be listed sorted by site treatment subject number, SOC and PT.

All medications will be listed by site treatment, subject number, start date, ATC level 1 and ATC level 2.

8 Exposure and Treatment Compliance

All tables in this section will be based on the ITT analysis set.

Categorical data will be summarised using numbers and percentages in addition to the sum 'all', the percentages are based on the total number of subjects with a corresponding assessment. Continuous data will be presented, using the number of subjects (n), mean and standard deviation, median, 25th percentile, 75th percentile, minimum and maximum.

8.1.1 Extent of Exposure

Total extent of exposure will be summarised. Total extent of exposure will be based on information from the vaginal ring administration log. For part A, the total extent of exposure will be the date of ring removal at the end of cycle 4 visit (if this visit is not performed or if no ring removal is performed at this visit the last date of ring removal is used) minus the date of the first ring insertion. For part B the extent of exposure will only be defined if the subject has completed part A and initiated part B (part A is considered completed if end-of cycle 4 visit is performed, part B is considered initiated if a ring is inserted at end-of-cycle 4 visit). The extent of exposure in part B is defined as the date of the last ring removal minus the date of end-of-cycle 4 visit.

Extent of exposure for each cycle (cycle 1 to 8) will also be summarised. Extent of exposure for each cycle will as above be calculated as the difference in ring removal dates and insertion dates.

8.1.2 Treatment Compliance

The treatment compliance in percent will be summarised. Treatment compliance will be based on information about missed dose from the medication errors log.

The compliance percent will be calculated as 100 times the ratio between the number of days exposed to the ring and the expected number of days exposed to the ring.

For part A: The expected number of days exposed to the ring is; if the subjects completes part A the date of end-of-cycle 4 visit minus the date the first ring insertion; and if the subject discontinues treatment during part A the date of discontinuation minus the date of visit 4. The number of days exposed to the ring is calculated as the expected number of days minus the number of days with missed dose between visit 4 and end-of cycle 4 visit (or if the subject discontinues during part A between visit 4 and date of discontinuation).

For part B: The expected number of days exposed to the ring is, if the subjects completes part B the date of end-of-cycle 8 visit minus the date of end-of-cycle 4 visit, and if the subject discontinues treatment during part B the date of discontinuation minus the date of

end-of cycle 4 visit. The number of days exposed to the ring is calculated as the expected number of days minus the number of days with missed dose between end-of cycle 4 visit and end-of-cycle 8 visit (or if the subject discontinues during part B between end-of-cycle 4 visit and date of discontinuation).

Non-compliance with IMP treatment regimen for >20% of days during a non-menstrual period, as defined as a protocol deviation in section 5 will be summarised for each cycle.

8.1.3 Listings

Based on the safety analysis set subjects the exposure data from the vaginal ring administration log and the medication errors log will be listed and the list will be sorted by site, treatment, subject number, and date. The listing will include information on dose, dates of insertion and removals, and type and timing of medication error.

9 Efficacy

9.1 Transformation of daily e-Diary data

Subjects will be ask to fill in the daily e-Diary every day from visit 1 to end-of-trial visit. Every night between 8 pm and 2 am the subject should answer the following question:

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

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

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

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

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.>

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

9.1.1 Definition of cycles

The e-Diary entries will be assigned to cycles in the following way.

The duration of cycle -2 is based on the menstruation dates log at visit 1 and visit 2. The date of the first day that belongs to cycle -2 is the start date of menses in the current cycle from visit 1 +7 days (note that if visit 1 is performed before this date there will be e-Diaries not assigned to a cycle, and if visit 1 is performed after this date there will be days in cycle -2 without an e-Diary). The last day that belongs to cycle -2 is the start date of menses in the current cycle from visit 2 +6 days.

The duration of the other cycles are defined in a similar way. The duration of cycle -1 is based on the menstruation dates log at visit 2 and visit 4. The duration of cycle 1 is based on the menstruation dates log at visit 4 and end-of-cycle 1 visit , and equivalently for cycle 2 to 10.If the start date of menses in the current cycle is missing at a visit, due to that the subject did not have menstrual bleeding just prior to that visit (the RM+7 visit in a cycle must be arranged within 35 days of the last RM+7 visit regardless of the subject has had menses). Then the two cycles from the RM+7 of previous, cycle to RM+7 of next cycle will be divided in two equally long cycles. E.g. if start date of menses in the current cycle is missing at end-of-cycle 2 visit (due to that the subject did not report menses), then cycle 2 will end and cycle 3 begin half way between start date of menses in the current cycle from end-of-cycle 1 visit and end-of-cycle 3 plus 7 days.

If the start date of menses in the current cycle in the menstruation log is missing for any other reason than the one mentioned above. Then the first date in that cycle where the subject answers yes to both question 9 and 11 in the e-Diary will be used instead.

9.1.2 Definition of menstrual period and non-menstrual period

Each cycle is divided into a menstrual period and a non-menstrual period, unless the subject does not have a menstrual bleeding during that cycle (see section 9.1.1), then the entire cycle will be considered non-menstrual.

The first day of menses is based on the start date of menses in the current cycle from the menstruation dates log. If this is missing for any other reason than the subject did not have menses in this cycle, then the first day in that cycle where the subject answers yes to both question 9 and 11 in the e-Diary will be used instead.

The last day of menses is based on the stop date of menses in the current cycle from the menstruation dates log. If the subject does have menses and the stop date is missing then the first day where the subject answers no to either question 9 or 11 in the e-Diary will be used instead. Note that the last day of menses could be in the next cycle relative to the first day of menses.

The menstrual period is defined as the period from the first day of menses to the last day of menses, both included.

The menstrual period of a cycle consists of the bleeding period in the end of the cycle plus the potential bleeding part in the beginning of the cycle. If a subject does not bleed in the end of the cycle, the entire cycles will be considered non-menstrual.

The non-menstrual part of the cycle is defined as the part of the cycle that is not considered the menstrual part.

9.1.3 Missing data for daily worst endometriosis-related pain question

If the subject do not complete the daily diary, then the day after the subject will be asked question 14 in the e-Diary. If the answer to question 14 is "I was in too much pain from endometriosis", the missing data for the previous day will be assigned a NRS of 10 for worst endometriosis-related pain (taking a worst-case approach). Otherwise, the daily score remains to be missing.

9.1.4 The mean daily NRS score

The baseline value for the mean daily NRS scores is defined as the average of the mean daily NRS scores of the two run-in cycles (cycles -2 and -1). For all post baseline cycles (cycles 1 to 10) the change in the mean daily NRS scores from baseline will be calculated using this definition of the baseline value.

9.1.4.1 The mean daily NRS score for worst endometriosis related pain

For each cycle, at least 50% of the NRS scores are required to be observed (including the imputed values as described in subsection 9.1.3) for both the menstrual period and the non-menstrual period (as defined in subsection 9.1.2) to be allowed to calculate the mean daily NRS score for that particular cycle. So if above 50% of the daily NRS scores are missing in either period of that cycle, the mean daily NRS score for worst endometriosis related pain for that cycle should be missing.

As missing daily NRS scores may not be appropriately balanced across menstrual period and non-menstrual period, the mean daily NRS score 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 number of days in the menstrual period of the cycle (as defined in subsection 9.1.2), l_{non-mp} is the number of days in the non-menstrual period of the cycle in question (as defined in subsection 9.1.2), $\bar{x}_{mp}$ is the mean daily NRS score based on the observed daily NRS scores (question 1) during the menstrual period (including imputations as described in 9.1.3), and $\bar{x}_{non-mp}$ is the mean daily NRS score (question 1) based on the observed daily NRS scores during the non-menstrual period (including imputations as described in 9.1.3).

If the subject does not have a menstrual period in a cycle the mean daily score is calculated as a simple mean, however if more than 50% of the daily NRS scores are missing the mean daily NRS will be considered missing

9.1.4.2 The mean daily NRS score for worst dysmenorrhea

For each cycle the mean daily NRS score for worst dysmenorrhea is defined as the mean daily NRS score for worst endometriosis related pain (question 1) during the menstrual period of that cycle (as defined in subsection 9.1.2).

If above 50% of the daily NRS scores in the menstrual period of a cycle are missing, the mean daily NRS score for worst dysmenorrhea for that cycle should be missing.

9.1.4.3 The mean daily NRS score for worst non-menstrual pelvic pain

For each cycle the mean daily NRS score for worst non-menstrual pelvic pain is defined as the mean daily NRS score for worst endometriosis related pain (question 1) during the non-menstrual period of that cycle (as defined in subsection 9.1.2).

If above 50% of the daily NRS scores in the non-menstrual period of a cycle are missing, the mean daily NRS score for worst non-menstrual pelvic pain for that cycle should be missing.

9.1.4.4 The mean daily NRS score for worst impact of endometriosis related pain on the subject ability to function

The mean daily NRS score for worst impact of endometriosis related pain on the subject ability to function will be based on the mean of question 5 to 8. The mean daily NRS score will be calculated if the mean daily NRS score for worst endometriosis related pain is calculated, it will be calculated using the same weighting scheme as used in section 9.1.4.1.

9.1.5 Analgesics use

Analgesic use will be used both as an endpoint by itself and as an adjustment variable for other endpoints. The baseline value for different measures of analgesics use is defined as the average of that measure in cycles -2 and -1.

9.1.5.1 Percentage of days with analgesics use

The percentage of days with analgesics use will be calculated for each cycle and separately for mild analgesics, strong analgesics and any analgesics. If the mean daily NRS score for worst endometriosis related pain is not calculated for a specific cycle due to many missing daily e-Diaries, then the three percentage of days with analgesics should not be calculated either.

The percentage of days with mild analgesics use is based on the first part of question 13. The percentage of days with strong analgesics use is based on the second part of question 13. The percentage of days with any analgesics use is based on both the first and the second part of question 13.

For adjustment of the secondary endpoints worst dysmenorrhea and worst non-menstrual pelvic pain similar variables will be needed for mild and strong analgesics just only using data from the e-Diary from the menstrual period and non-menstrual period of the cycle, respectively. If the mean daily NRS for worst dysmenorrhea or worst non-menstrual pelvic pain is not calculated due to to many missing variables the corresponding percentage of days with mild analgesics should not be calculated either.

9.1.5.2 Total and average doses of analgesics

For each cycle the total dose of mild analgesics is calculated by summing the daily doses from the first part of question 13 (if the answer is no, then the dose is 0 mg). For each cycle the total dose of strong analgesics is calculated by summing the daily doses from the second part of question 13 (if the answer is no, then the dose is 0 mg). The average doses are calculated as the total dose divided by the number of times question 13 has been answered during that cycle.

The total and average doses will be calculated if the mean daily NRS score for worst endometriosis related pain is calculated, it will be calculated using the weighting scheme as described in section 9.1.4.1.

9.1.6 Responder status

Twelve different definitions of responder status are being used in this trial, one for each combination of the 4 mean daily NRS score defined in section 9.1.4 and the 3 thresholds ≥30%, ≥50% and ≥70%.

A subject is defined as being a responder in a specific cycle if the mean daily NRS score is reduced with at least the threshold value compared to baseline and that the percentage of days on any analgesics has not increased by more than 10% since baseline.

9.1.7 Dyspareunia

9.1.7.1 The mean daily NRS score for worst dyspareunia

For each cycle, the mean daily NRS score for worst dyspareunia is calculated as the mean of the worst pain during or after sexual intercourse (question 4) for that cycle. There are no minimal requirements on the number of times question 4 is answer for the mean to be calculated.

9.1.7.2 Frequency of avoiding sexual intercourse

For the analysis of frequency of avoiding sexual intercourse, two variables are needed, firstly the number of days during that cycle that the subject avoids sexual intercourse because of expected pain (that is how many times the subject answers yes to question 3) is needed. Secondly the number of days during that cycle that the subject does not avoid having sexual intercourse because of expected pain (that is how many times the subject answers yes to question 2 or no to question 3) is needed.

9.1.8 Vaginal bleeding pattern

The vaginal bleeding pattern is evaluated as the number of days per cycle with no bleeding, spotting, light bleeding, moderate bleeding and heavy bleeding days, respectively. Additionally the duration of menstrual and non-menstrual period, and the number of bleeding days during the non-menstrual period, will be calculated.

9.2 Transformation of weekly e-Diary data

Subjects will be asked to fill in the weekly e-Diary every week from visit 1 to end-of-trial visit. Every week between Sunday 8 pm and Tuesday 2 am the subject should answer the following question:

Instructions and the question to be answered are:

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?	☐	☐	☐	☐	☐

The additional work item (Question 12) 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 weekly EHP-30 pain impact score will be calculated based on question 1 to 11 in the following way, a raw score will be calculated as the sum of scores from each question were an answer of never will be scored as 0, rarely as 1, sometimes as 2, often as 3, and always as 4. This raw score will then be multiplied with 100 and divided by 44, (So that the score will be between 0 and 100, 0 indicating the best health status and 100 the worst health status).

The weekly EHP-30 pain impact score will assigned to cycles in the following way. The week mentioned in the questionnaire as last week will be regarded as the week starting on a Monday and ending on the Sunday where the questionnaire is opened for access, both days included. The weekly score will be assigned to the cycle that cover most of that week. So if the first day of the current cycle (the cycle that includes the Sunday where the questionnaire is opened for access) is on the Thursday of that week or before the week will be assigned to the current cycle. If the first day of the current cycle is on the Friday of that week or later the week will be assigned to the previous cycle.

The mean weekly score is calculated as a simple mean of the weekly scores assigned to that cycle. The mean weekly scores will be calculated as long at least one weekly score is not missing. The baseline weekly score is the average of the two mean weekly scores from cycle -2 and cycle -1.

9.3 General Considerations

All efficacy endpoints will be summarised by treatment using descriptive statistics. Categorical data will be summarised using numbers and percentages (n and % of all observed) in addition to the sum 'All', the percentages are based on the total number of subjects with a corresponding assessment in the analysis set. Continuous data will be presented, using the number of subjects (n), mean and standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum. The primary endpoint will be summarized using both the ITT population and the PP population, all other endpoints will be summarized using only the ITT population.

As the trial has been prematurely discontinued, it has been decided, due to the low number of subjects, that no statistical analysis will be performed, see section 1 and 12.

9.3.1 Efficacy and exploratory endpoints

For the primary endpoint, each of the secondary, and each of the exploratory endpoints mentioned in Table 9-1 the absolute value at baseline and the absolute value at cycle 1 to 4 (if appropriate), and the change from baseline at cycles 1 to 4 (if appropriate) will be summarised by treatment.

Table 9-1 Efficacy and Exploratory Endpoints

Endpoint
Changes in the mean daily NRS scores for the worst endometriosis-related pain at cycle 4
Changes in the mean daily NRS scores for the worst endometriosis-related pain over 8 menstrual cycles
Changes in the mean daily NRS scores for the worst dysmenorrhea and for the worst non-menstrual pelvic pain over 8 menstrual cycles
Changes in the mean daily NRS scores for the worst dyspareunia on days with sexual intercourse over 8 menstrual cycles
Frequency of avoiding sexual intercourse due to expected pain over 8 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 8 menstrual cycles
Changes in the mean weekly scores of the EHP-30 pain impact domain over 8 menstrual cycles
Changes in vaginal bleeding pattern over 8 menstrual cycles
Percentage of days with mild and/or strong rescue analgesics used over 8 menstrual cycles
Total and average doses of mild and/or strong rescue analgesics used over 8 menstrual cycles
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 8 menstrual cycles
Changes in the mean individual and total symptom and sign severity scores of the B&B scale at cycles 4 and 8
Changes in EHP-30 scores over 8 menstrual cycles
Changes in PGIS scores at cycles 4 and 8
PGIC scores at cycles 4 and 8
Serum levels of mid-luteal phase progesterone [f], estradiol, prolactin, TSH and IGF-1 at cycles 4

9.4 Analysis of Pharmacokinetics

The pharmacokinetic data will be reported elsewhere.

10 Safety

10.1 General Considerations

Safety parameters will be evaluated for the safety analysis data set.

All safety summaries will be performed by treatment:

For adverse events (AE) and concomitant medications the following rules will apply;

Treatment period	AE and concomitant medications to be included
Part A	Start after start of IMP, and start date before or equal to the date of the end-of-cycle 4 visit, if missing use date of premature discontinuation
Part B	Start date after the date of the end-of-cycle 4visit and before or equal to date last ring removal, if missing use date of premature discontinuation.

10.2 Adverse Events

AEs are classified according to MedDRA version 20.0.

Written narratives will be issued for all serious AEs (including deaths) and AEs leading to withdrawal.

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. Pre-treatment AEs will be presented in a separate data listing only.

A treatment-emergent adverse event (TEAE) 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.

10.2.1 Overview of Treatment-Emergent Adverse Events

An AE overview summary table will be prepared including the number of subjects reporting an AE, the percentage of subjects (%) with an AE, and the number of events (E) reported, for the following categories:

- All TEAEs

- TEAEs leading to Deaths
- Serious TEAEs
- TEAEs leading to withdrawal
- Adverse drug reactions (as assessed by investigator)
- Serious Adverse drug reactions

10.2.2 Incidence of Adverse Events

Treatment-emergent adverse events will be summarised

The tables will display the total number of subjects reporting an AE, the percentage of subjects (%) with an AE, and the number of events (E) reported. AEs will be presented by SOC sorted alphabetically and PT sorted in decreasing frequency of occurrence.

Summary tables will be prepared for:

- All treatment emergent adverse events
- Treatment emergent adverse events with an incidence ≥ 5% of subjects in any treatment group
- Treatment emergent related adverse events
- Treatment emergent related serious adverse events
- Treatment emergent non serious adverse events with an incidence ≥ 5% of subjects in any treatment group
- Treatment emergent unrelated adverse events
- Treatment emergent adverse events leading to death
- Treatment emergent adverse events leading to withdrawal
- Treatment emergent mild adverse events
- Treatment emergent moderate adverse events
- Treatment emergent severe adverse events
- Treatment emergent related mild adverse events
- Treatment emergent related moderate adverse events
- Treatment emergent related severe adverse events
- Treatment emergent serious adverse events

Supporting data listings will be provided for:

- All adverse events sorted by centre and subject no.
- All adverse events sorted by MedDRA Preferred Term
- Serious adverse events
- Adverse events leading to death
- Adverse events leading to withdrawal.

The listings will include information whether the AE occurred during the COVID-19 trial hold.

10.2.3 Incidence of Adverse Events of Special Interest

10.2.3.1 Dizziness/Pre-syncope

Treatment-emergent adverse events of dizziness/pre-syncope will be summarised, similar to the tables described in 10.2.2. Two tables will be prepared one with all TEAE and one with related TEAE(as assessed by the investigator). An AE is considered to be dizziness/pre-syncope if the PT is included in the list below:

Dizziness
Dizziness postural
Dizziness exertional
Persistent postural-perceptual dizziness
Procedural dizziness
Pre-syncope
Vertigo
Vertigo positional
Vertigo CNS origin

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

Dysmenorrhea, Abdominal Pain, Pelvic Pain, Lower Back Pain and Dyspareunia is reported as part of the efficacy reporting.

10.2.3.3 Vaginal bleeding

Vaginal bleeding is reported as part of the efficacy reporting

10.2.3.4 Syncope

Treatment-emergent adverse events of syncope will be summarised, similar to the tables described in 10.2.2. Two tables will be prepared one with all TEAE and one with related TEAE (as assessed by the investigator). An AE is considered to be syncope if the PT is included in the list below:

Syncope
Loss of consciousness
Altered state of consciousness

10.2.3.5 Vaginal Irritation and/or Vaginal Infection

Treatment-emergent adverse events of Vaginal Irritation and/or Vaginal Infection will be summarised, similar to the tables described in 10.2.2. Two tables will be prepared one with all TEAE and one with related TEAE(as assessed by the investigator). An AE is considered to be Vaginal Irritation and/or Vaginal Infection if the High level term is included in the list below:

vulvovaginal signs and symptoms
vaginal and vulval infections and inflammation

10.3 Safety Laboratory Variables

Baseline for all laboratory analyses will be the values obtained at the last assessment prior to the first dose of the investigational medicinal product (IMP). Treatment-emergent laboratory data will include tests completed after the first dose of IMP through the residual time of drug effect. End of trial will include the last post-baseline observation during the trial. Safety lab values are planned to be measured four times, at baseline, at end of part A, at end of party B, and at end of trial. In case of premature discontinuation an extra measurements is planned. If premature discontinuation is during part A the extra measurement will be used both as end of part A and end of trial measurement, if premature discontinuation is during part B the extra measurement is used as both end of part B and end of trial measurement

Laboratory variables will be grouped under “Haematology”, “Clinical Chemistry” or “Urinalysis”

10.3.1 Summary Statistics

Mean change and mean percentage (%) change from baseline at end of trial will be presented for each laboratory variable. In addition, descriptive statistics, i.e., the number of subjects with data, mean (standard deviation), median, minimum, and maximum values, will be presented for observed values and change from baseline at each time-point for each laboratory variable.

10.3.2 Laboratory Variable Changes Relative to Normal Range

As the trial has been prematurely discontinued, it has been decided, due to the low number of subjects, that no shift tables will be prepared. Clinical significant changes in laboratory values are presented in the AE tables.

10.3.3 Data Listings

Data listings will be prepared by treatment for all subjects with any abnormal laboratory value at any time-point (including screening, baseline).

10.3.4 Urinalysis

Incidence of changes in urinalysis will be summarised. Summary tables with number of subjects with change from *Absent* at baseline to *Present* during trial will be summarised.

10.4 Vital Signs and ECG

10.4.1 Vital Signs

Baseline for all vital signs analyses will be the values obtained at the last assessment prior to the first dose of IMP. Treatment-emergent vital signs data will include tests completed after the first dose of IMP through the time of residual drug effect. End of trial will include the last post-baseline observation during the trial.

10.4.1.1 Summary Statistics

Mean change and mean percentage (%) change from baseline at end of trial will be presented for each vital signs variable. In addition, descriptive statistics, i.e., the number of subjects with data, mean (standard deviation), median, minimum, and maximum values, will be presented for observed values and change from baseline at each time-point for each vital signs variable.

10.4.1.2 Data Listings

Data listings will be prepared by centre for all subjects with any abnormal vital signs value at any time-point (including screening, baseline).

10.4.2 ECGs

The 12-lead ECG will be recorded prior to randomization at cycle -1 (visit 4), at cycles 4 and 8. Results at randomization will be used as baseline. The ECG will be recorded with a calibrated ECG device after the subject has been in supine position for at least 5 minutes.

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= $QT/RR^{0.33}$, calculated automatically in the e-CRF). ECG recordings will capture at least four QRS complexes, i.e. 3 evaluable RR intervals. The investigator will evaluate whether the ECG is normal or abnormal and if abnormal, whether it is clinically significant. ECG may be repeated for quality reasons and in this case the repeated assessment will be used for analysis.

10.4.2.1 Summary Statistics

Descriptive statistics, i.e., the number of subjects with data, mean (standard deviation), median, minimum, and maximum values, will be presented for observed values and change from baseline at each time-point for each ECG variable.

10.4.2.2 Data Listings

Data listings will be prepared by treatment and site for all subjects with any abnormal ECG value at any time-point.

10.5 Other Safety Variables

10.5.1 Changes in Bone-turnover Markers

Changes in bone-turnover markers will be summarised.

10.5.2 Echocardiography

The proportion of subjects with clinically significant echocardiography findings will be tabulated by treatment.

10.5.3 Impulsive-Compulsive Disorders

Frequency-tables for each item of the questionnaire for impulsive-compulsive disorders as well as the proportion of subjects having potential behaviours associated with impulse control disorders will be summarized by treatment.

Treatment-emergent adverse events potentially related to behaviours associated with impulse control disorder will be summarised, similar to the tables described in 10.2.2. An AE is considered to potentially related to behaviours associated with impulse control disorder if the PT is included in the SMQ hostility/aggression (broad) or included in the list of PTs below:

Alcohol abuse
Alcohol problem
Alcohol use
Behavioural addiction
Binge drinking
Binge eating
Compulsions
Compulsive hoarding
Compulsive sexual behaviour
Compulsive shopping
Disturbance in sexual arousal
Dopamine dysregulation syndrome
Drug abuse
Drug abuser
Eating disorder
Economic problem
Emotional disorder
Emotional distress
Euphoric mood
Excessive masturbation
Exhibitionism
Gambling
Gambling disorder
Gaming disorder
High risk sexual behaviour
Hyperphagia
Hypersexuality
Increased appetite
Judgement impaired
Kleptomania
Libido disorder
Libido increased
Male orgasmic disorder
Mental disorder
Mental status changes
Mood altered
Mood swings
Obsessive rumination
Obsessive thoughts
Obsessive-compulsive disorder
Obsessive-compulsive personality disorder
Obsessive-compulsive symptom
Overconfidence
Poriomania
Promiscuity
Pseudologia
Restlessness
Self-esteem inflated
Sexual activity increased
Sexually inappropriate behaviour
Stereotypy
Thinking abnormal
Weight increased

10.5.4 Ring Acceptability

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

11 Interim Analyses

An interim analysis with the option to stop the trial early due to futility was planned, but as the trial was prematurely discontinued, this interim analysis was not performed

The trial was terminated early. The decision was taken due to the results from the parallel phase 2 trial in Europe (Trial 000295) and the continued difficulties with subject recruitment.

Due to the low number of subjects recruited, no interim analysis was performed, and no statistical analysis was performed. Instead results are presented as descriptive statistics by treatment group separately for Part A and Part B.

Furthermore, due the low number of subject the shift tables and tables displaying proportions of subjects with markedly abnormal values for the safety endpoint will not be prepared, the information on change from baseline can be assessed using the listings.

12 Deviations from Protocol Analysis

The trial was terminated early. The decision was taken due to the results from the parallel phase 2 trial in Europe (Trial 000295) and the continued difficulties with subject recruitment.

Due to the low number of subjects recruited, no interim analysis was performed, and no statistical analysis was performed. Instead results are presented as descriptive statistics by treatment group separately for Part A and Part B.

Due the low number of subjects the shift tables and tables displaying proportions of subjects with markedly abnormal values for the safety endpoint will not be prepared, the information on change from baseline can be assessed using the listings.

Due to the low number of subjects the proportion of subjects with serum levels of mid-luteal progesterone ≥25 nmol/, and the endometriosis biomarkers will not be summarized