Cover page for Statistical Analysis Plan

Sponsor name	Ferring Pharmaceuticals A/S
NCT Number	NCT03749109
Sponsor trial ID:	000295
Official title of study	A randomised, double-blind, placebo-controlled, proof-of-mechanism phase 2 trial investigating the effect of quinagolide extended-release vaginal ring on reduction of lesions assessed by high-resolution magnetic resonance imaging in women with endometrioma, deep infiltrating endometriosis, and/or adenomyosis
Document Date	26 August 2021

STATISTICAL ANALYSIS PLAN

QLARITY
Quinagolide Vaginal Ring on Lesion Reduction Assessed by MRI in Women with Endometriosis/Adenomyosis
A randomised, double-blind, placebo-controlled, proof-of-mechanism phase 2 trial investigating the effect of quinagolide extended-release vaginal ring on reduction of lesions assessed by high-resolution magnetic resonance imaging in women with endometrioma, deep infiltrating endometriosis, and/or adenomyosis

Trial 000295

Investigational Medicinal Product: FE 999051, Quinagolide Vaginal Ring

Indication: Endometriosis

Phase: 2

Author: [redacted]

Date of issue: 26AUG2021

Version: 1.0

TABLE OF CONTENTS

List of Tables

List of Figures

1 Introduction

This document describes the planned statistical analyses for Trial 000295, and is based on version 4.0 of the clinical trial protocol dated 12th of November 2019.

1.1 Definitions/ Abbreviations

1.1.1 Definition of Terms

Terms	Definitions
Randomised	Subject randomised to trial treatment
Screened	Subject who enters the screening phase

1.1.2 Abbreviations

Abbreviations	Meaning of abbreviations in document
FAS	Full analysis set
PP	Per-Protocol
IMP	Investigational Medicinal Product
DIE	deep infiltrating endometriosis
MRI	magnetic resonance imaging
TVU	transvaginal ultrasound
NRS	Numerical Rating Scale
EHP-30	Endometriosis Health Profile-30
B&B	Biberoglu and Behrman
MedDRA	Medical Dictionary for Regulatory Activities
RM	Return of menses
ANCOVA	Analysis of covariance
GEE	Generalized estimating equation
SOC	System organ class
PT	Preferred term
PROs	Patient reported outcomes
TSH	Thyroid-stimulating hormone
MCMC	Markov chain Monte Carlo
MNAR	Missing not at random
MAR	Missing at random
MI	Multiple imputation
AE	Adverse events
TEAE	Treatment emergent adverse events
ADR	Adverse drug reactions
RMP	Risk management plan

2 Trial Objectives and Endpoints

2.1 Objectives

2.1.1 Primary Objective

- To evaluate the effect of quinagolide vaginal ring compared to placebo on reduction of lesions for endometrioma, deep infiltrating endometriosis (DIE) and adenomyosis assessed by high-resolution magnetic resonance imaging (MRI)

2.1.2 Secondary Objectives

- To evaluate the effect of quinagolide vaginal ring compared to placebo on reducing the sizes of endometrioma assessed by transvaginal ultrasound (TVU)
- To evaluate the effect of quinagolide vaginal ring on patient reported outcomes (PROs)
- To evaluate the plasma concentrations of quinagolide and its metabolites
- To evaluate the effect of quinagolide vaginal ring on serum endocrine parameters
- To evaluate the effect of quinagolide vaginal ring on menstrual bleeding pattern
- To evaluate the safety profile of quinagolide vaginal ring including adverse events and routine safety laboratory parameters

2.1.3 Exploratory Objectives

- To explore the effect of quinagolide vaginal ring on the MRI-derived perfusion imaging biomarkers of angiogenesis and on the MRI-derived diffusion imaging biomarkers of lesion tissue structure
- To explore the effect of quinagolide vaginal ring on reducing the size of uterine fibroids assessed by both MRI and TVU
- To explore the effect of quinagolide vaginal ring on endometriosis biomarkers

2.2 Endpoints

2.2.1 Primary Endpoint

- Changes in the sizes (mm) of endometrioma, DIE and adenomyosis lesions summed by type on MR images at cycle 4

2.2.2 Secondary Endpoints

- Percentage of changes in the sizes of endometrioma, DIE and adenomyosis lesions summed by type on MR images at cycle 4
- Proportion of lesions by type with a decrease in a size of ≥5 mm on MR images at cycle 4
- Proportion of subjects with a lesion of any type decreased in a size of ≥5 mm on MR images at cycle 4
- Number of new or disappearing endometrioma, DIE and adenomyosis lesions summed by type on MR images at cycle 4
- Changes in the volumes (mm^3) of endometrioma and DIE lesions summed by type on MR images at cycle 4
- Changes in the sizes of endometrioma assessed by TVU at cycle 4
- Changes in the mean individual and total symptom and sign severity of scores of the Biberoglu and Behrman (B&B) scale at cycle 4
- Changes in the Numerical Rating Scale (NRS) pain scores per cycle at cycles 1, 2, 3 and 4
- Changes in the Endometriosis Health Profile-30 (EHP-30) scores at cycles 2 and 4
- Changes in the menstrual bleeding pattern over 4 cycles
- Serum levels of prolactin, thyroid-stimulating hormone (TSH), insulin-like growth factor-1 (IGF-1) during cycle 1, at cycles 2 and 4
- Plasma concentrations of quinagolide and its metabolites during cycles 1 to 4
- Changes in clinical chemistry and haematology parameters and proportion of subjects with markedly abnormal changes
- Frequency and intensity of adverse events

2.2.3 Exploratory Endpoints

- Changes in the MRI-derived perfusion imaging biomarkers of AUC, K^{trans}, k_{ep}, v_e, v_p at cycle 4 (The analysis of these endpoints will not be described in this SAP, as it will be reported separately)
- Changes in the MRI-derived diffusion imaging biomarkers of ADC, D, D* and f at cycle 4 (The analysis of these endpoints will not be described in this SAP, as it will be reported separately)
- Changes in the sizes of uterine fibroids on MRI at cycle 4
- Changes in the sizes of uterine fibroids assessed by TVU at cycle 4
- Changes in circulating levels of vascular endothelial growth factor (VEGF), placental growth factor (PlGF), interleukin 6 (IL-6), cancer antigen 125 (CA125) and soluble fms-like tyrosine kinase 1 (sFlt-1) at cycle 4

3 Trial design

This is a randomised, double-blind, placebo-controlled, phase 2 trial investigating the effect of quinagolide extended-release vaginal ring on reduction of lesions, assessed by high-resolution MRI, in women with endometrioma, DIE and/or adenomyosis.

3.1 Overall Trial Design

In this trial, quinagolide vaginal ring or placebo vaginal ring will be administered sequentially for four menstrual cycles, where a menstrual cycle is considered the period between day 7 after return of menses (RM+7) in a cycle until the following day 7 after return of menses of the next cycle. The RM+7 visits in this trial can be scheduled within the period of 6-10 days after return of menses (RM+6-10).

The trial consists of the following periods:

1) Screening: starting from the signing of informed consent to randomisation (≤3 cycles) and including a wash-out period (only applicable to subjects using some hormonal contraceptives) and a screening cycle (cycle -1, applicable to all subjects)
2) Treatment: double-blind, placebo-controlled treatment with quinagolide vaginal ring or placebo vaginal ring administered sequentially for four menstrual cycles (cycles 1, 2, 3 and 4)
3) Follow-up: about 1 month after end-of-treatment

Screening: Subjects should be screened for eligibility within approximately 4 months of randomisation. Subjects who are currently using some hormonal products (e.g. combined oral contraceptive pill, progestogen and levonorgestrel-releasing intrauterine device (IUD)) may be eligible for the trial if they have completed the wash-out period and have return of menses.. In this case, subjects need to sign the informed consent before they discontinue those products. Discontinuation of the products should follow their labelling (e.g. completing the current cycle of contraceptives before discontinuation). Subjects who are not using exclusionary hormonal products can enter the screening cycle directly. Prescriptions of analgesics for pain management are allowed in this trial.

After having completed the wash-out period (if applicable) and having RM, subjects will attend the screening RM+7 visit to undergo initial screening assessments, including a MRI examination by a high resolution 3-tesla (3T) machine. Depending on facilities at sites, MRI may not necessarily be scheduled at the same screening visit, but it must be scheduled on a day without bleeding to avoid biases and to ensure the availability of the central MRI reading report prior to randomisation. The MRI at screening, used as baseline, should not be obtained more than 1 menstrual cycle before randomisation.

Eligible subjects must have at least one of the following three types of lesions with the following sizes identified by MRI: endometrioma (≥20 mm), DIE (≥15 mm), and/or adenomyosis (maximum junctional zone thickness ≥12 mm or focal lesion ≥15 mm). If a subject has more than one type of lesions, she will be grouped under the more rare type in the ranking of DIE, adenomyosis and endometrioma. For example, a subject with both DIE and endometrioma will be included in the DIE sub-group but both types of lesions should be measured. Every measurable lesion (defined as ≥10 mm in size) of any type should be recorded and should be summed up by type for primary analysis. For DIE and endometrioma, lesions will be measured both in size and in volume. For uterine fibroid, only size will be measured. Size will be recorded in mm as the longest diameter in the plane of measurement. Volume will be recorded in mm^3 using a semi-automated method based on 3D region-growing algorithm, adjusted with manual correction. For adenomyosis, the maximum junctional zone thickness (applicable to diffuse adenomyosis) or the size of the largest focal lesion (applicable to focal adenomyosis) will be measured. All MRIs should be uploaded into a specific image repository allocated for this trial within 2 business days for central reading and analyses by a specialised imaging laboratory. Subject eligibility with regard to inclusion criterion no. 6 must be determined based on the central MRI reading report.

Subjects are required to fast for 3-4 hours before the MRI examination. The preparations for MRI examination should follow the trial-specific MRI manual. The MRI procedures will include the following main sequences:

- Fast spin echo – T2-weighted images (FSE-T2)
- Diffusion weighted (DW-IVIM) images with more than 2 b-values
- Gradient echo (GRE) – T1-weighted images with varying flip angles (GRE-T1-VFA)
- Dynamic, contrast-enhanced, spoiled GRE T1-weighted images (DCE-PKM-Gd)
- Late gadolinium enhancement spoiled GRE T1-weighted images (GRE-T1-LATEGd)

Other details for the MRI examination will be specified in the MRI manual. Prior to the start of the trial, site radiologists will be trained on the MRI manual. Site radiologists must follow the MRI manual for the preparation and the execution of the MRI assessment.

In addition to MRI, a TVU should be performed at the screening RM+7 visit to assess uterus, endometrium, and ovaries and to measure the size(s) of any endometrioma and/or fibroid.

Subjects will be required to use a non-hormonal single-barrier method for contraception (i.e. condom) from screening to end-of-treatment.

Treatment: Eligible subjects in each sub-group will be randomised at the end of cycle -1 in to receive quinagolide vaginal ring or placebo vaginal ring for four menstrual cycles (cycles 1, 2, 3 and 4). The study was planned to be have a randomisation ratio of 2:1 with 2 subjects receiving quinagolide vaginal ring for each subject receiving placebo vaginal ring, however it was discovered, after LPLV but before database lock, that the randomisation list used during the study had a 1:1 ratio between quinagolide vaginal ring and placebo vaginal ring. Approximately 24 subjects will be

randomised in each sub-group, adding up to a total of 72 subjects in this trial. Quinagolide vaginal ring contains a dose load of quinagolide 1080 µg at a target daily release rate of quinagolide 13.5 µg.

After randomisation, subjects will self-insert the assigned ring in the upper part of the vagina at sites 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 by the next ring at RM+7 visit of the next cycle.

Subjects who have discontinued during or after cycle 2 should come for an end-of-treatment visit with MRI, scheduled within 2 weeks of discontinuation. Subjects who have completed the scheduled treatment should come for an MRI examination at or close to the RM+7 visit of cycle 4. The MRI at end-of-treatment / cycle 4 must be performed using the same machine, following the same procedures and sequences as at screening (detailed in the MRI manual).

To measure permeability, perfusion imaging biomarkers of the one-compartmental metric (AUC) and the two-compartmental metrics (K^{trans}, k_{ep}, v_e, v_p) will be derived from the dynamic perfusion series. In addition, diffusion metrics (ADC, D, D* and f) of lesion tissue structure will be obtained using the intra-voxel incoherent motion (IVIM) model. All perfusion and diffusion parameters at screening and at end-of-treatment will be assessed and analysed by the central imaging laboratory. All lesions will be segmented in 3D by two radiologists for the analyses of imaging biomarkers.

TVU will be performed at end-of-treatment / cycle 4, preferably by the same sonographer as at screening, to measure the sizes of endometrioma and/or uterine fibroid.

B&B will be administered at baseline and at end-of-treatment / cycle 4, with trial coordinators completing the first part based on subjects' verbal response and investigators completing the second part based on findings of a pelvic examination. At each RM+7 visit from randomisation to cycle 4, subjects will score the worst pain they experienced during the past menstrual cycle on a self-administered NRS, with 0 indicating no pain and 10 indicating worst imaginable pain. In addition, they will complete the EHP-30 questionnaire at randomisation, at cycle 2 and at end-of-treatment / cycle 4. All PROs will be administered on paper at sites.

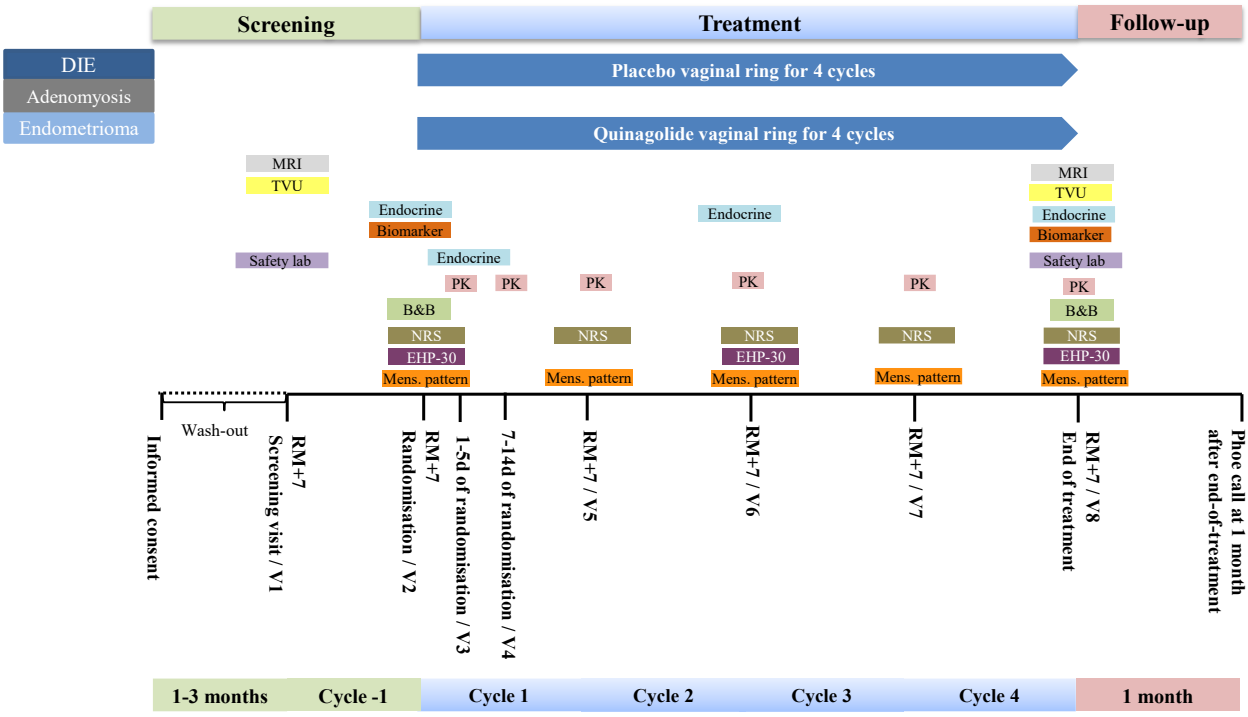
At each RM+7 visit from randomisation to end-of-treatment / cycle 4, the site staff should inquire about the bleeding pattern of the subject's immediate past menstrual period, including the start and stop dates (if available) of menstrual bleeding and the amount of menstrual flow.

Blood samples are collected throughout the trial for the purpose of evaluating endocrine profile, plasma concentrations of quinagolide and its metabolites, routine safety laboratory parameters as well as endometriosis biomarkers. Endocrine parameters, consisting of prolactin, TSH and IGF-1, will be assessed at randomisation, within 1-5 days of randomisation, at cycle 2 and at end-of-treatment / cycle 4. To measure the plasma concentrations of quinagolide and its metabolites, blood samples will be taken within 1-5 days of randomisation, within 7-14 days of randomisation and prior to ring removal at RM+7 visits of cycles 1 to 4. Routine safety laboratory tests for clinical

chemistry and haematology parameters will be performed at screening and at end-of-treatment / cycle 4. Blood samples for serum and plasma endometriosis biomarkers of VEGF, PlGF, IL-6, CA125 and sFlt-1 will be collected at randomisation and at end-of-treatment.

Follow-up: A telephone call will be made to all subjects at about 1 month after the end-of-treatment / cycle 4 visit to collect information about adverse events and concomitant medications since the visit, and reasons for resuming medications indicated for endometriosis / adenomyosis.

3.1.1 Trial Diagram



Abbreviations: B&B=Biberoglu and Behrman Scale, d=day(s), DIE=deep infiltrating endometriosis, EHP-30=Endometriosis Health Profile 30 Questionnaire, Mens. pattern=menstrual bleeding pattern, MRI=magnetic resonance imaging, NRS=Numerical Rating Scale, PK=pharmacokinetic(s), RM=return of menses, RM+7=day 7 after return of menses, TVU=transvaginal ultrasound, V=visit

Figure 3-1 Trial Diagram – Trial Period

3.1.2 Trial Flow Chart

Table 3-1 Trial Flow Chart – Procedures at Clinic Visits

	Screening [a,b]			Treatment Period [b]						Follow-up
	Wash-out [a]	Cycle -1 start	Cycle -1 end	Cycle 1			Cycle 2	Cycle 3	Cycle 4	
		Screening visit (V1)	Randomi-sation (V2)	V3	V4	V5	V6	V7	V8	Phone call
	~1-3 months before V1	RM+7	RM+7	1-5 days of V2	7-14 days of V2	RM+7	RM+7	RM+7	RM+7 / EOT	~1 month after V8
Written informed consent	X[a]	X[a]								
Inclusion/exclusion criteria	X[a]	X	X[c]							
Demographics		X								
Medical/menstrual/repro history		X								
Body measurements		X								
Vital signs		X	X[c]	X					X	
Physical examination		X							X	
Gynaecological examination		X							X	
Cervical cytology [d]		X								
Transvaginal ultrasound (TVU) [f]		X							X	
Urine pregnancy test [g]		X	X[c]			X[h]	X[h]	X[h]	X[h]	
Randomisation			X							
Blood sample (safety)		X				X[i]			X	
Blood samples (endocrine)			X[h]	X			X[h]		X[h]	
Blood samples (biomarkers)			X[h]						X[h]	
Blood sample (PK)				X	X	X[h]	X[h]	X[h]	X[h]	
MRI		X[e]							X[e]	
B&B scale			X[h]						X[h]	
NRS			X[h]			X[h]	X[h]	X[h]	X[h]	
EHP-30 questionnaire			X[h]				X[h]		X[h]	
Vaginal ring dispensing			X			X	X	X		
Insertion (i) / removal (r) of ring			i			i,r	i,r	i,r	r	
Drug accountability						X	X	X	X	
Menstrual bleeding pattern			X			X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X
Condom dispensing / reminder		X	X	X	X	X	X	X		
End-of-treatment form									X	

B&B=Biberoglu and Behrman Scale, EHP-30=Endometriosis Health Profile 30 Questionnaire, EOT=end-of-treatment, i=insertion, NRS=Numerical Rating Scale, PK=pharmacokinetic(s), r=removal, RM+7=day 7 after return of menses, V=visit.

a Subjects who are currently using some hormonal contraceptives (including combined oral contraceptive pill, transdermal patch and contraceptive ring) may be eligible for the trial if they have completed the wash-out period (if applicable) and have return of menses. In this case, subjects need to sign the informed consent before the wash-out. Subjects not requiring wash-out will sign the informed consent at the screening visit.

b A menstrual cycle in this trial is considered the period between RM+7 in a cycle until the following RM+7 in the next cycle. The RM+7 visit can be scheduled 6-10 days after return of menses (RM+6-10) and is always at the end of each cycle. An exception is cycle -1 which starts with RM+7 of a prior cycle.

c Performed before randomisation.

d Performed only for subjects who do not have a cervical cytology test result within 24 months of the screening visit.

e Performed at or close to the RM+7 visit at screening and at cycle 4 when the subject has no bleeding and no ring. Performed using the same machine, following the same procedures and sequences (see MRI manual). Fasting for 3-4 hours in advance. Subjects prematurely discontinued during or after cycle 2 should also come for an end-of-treatment visit with MRI, scheduled within 2 weeks of discontinuation.

f Performed preferably by the same sonographer. Size(s) of endometrioma and/or uterine fibroid, if any, should also be measured.

g If the urine pregnancy test is positive, blood collection for a serum βhCG test at the local laboratory must be performed.
h Performed before ring insertion and/or removal, with PROs performed prior to other non-PRO procedures.
i Performed only at Italian sites.

3.2 Data presentation

Due to the trial design including separate analysis of the primary endpoint for each of the three types of lesion (endometrioma, DIE and adenomyosis), some presentations will be performed by type of lesion, some will be performed for the three types of lesions combined, and some will be performed both by type and combined. Additionally, some presentations are also prepared by type of disease (i.e. endometriosis and adenomyosis), where the category of endometriosis combines endometrioma and DIE.

A subject will be included in the by type analysis if she has at least one lesion of that type ≥10 mm at baseline. Notice that a subject can be included in the analysis of more than one type of lesions.

3.3 Determination of Sample Size

The sample size calculation is based on demonstrating superiority of quinagolide vaginal ring compared to placebo vaginal ring on the primary endpoint of changes in the sizes of endometrioma, DIE and adenomyosis lesions summed by type on MRI at cycle 4. An important assumption behind the sample size calculation is an equal magnitude of treatment effect for all three types of lesions. For example, for adenomyosis, by assuming an average baseline lesion size of 18 mm and a standard deviation of 4.5 mm [1], a sample size of 24 randomised subjects (16 on active treatment and 8 on placebo) will have 83% power to detect a treatment effect difference of 6 mm (corresponding to a 33% reduction in lesion size) using a two-sample t-test at a 5% two-sided significance level. A similar assumption, i.e. the ratio between treatment effect and standard deviation is 4 to 3, is made for DIE and endometrioma to conclude 24 subjects to be randomised per sub-group. In total, 72 subjects will be randomised in this trial.

Table 3-2 Sample Size by Treatment Effect Difference

Difference in the sum of lesion size reduction between quinagolide vaginal ring group and placebo vaginal ring group		Number of subjects in total [a]	
Absolute difference (mm)	**Relative difference [b] (%)**	**Power 80%**	**Power 90%**
4.5	25	39	51
5.0	28	33	42
5.5	31	27	36
6.0	33	24	30
6.5	36	21	27
7.0	39	18	24
7.5	42	15	21

a Using a 2:1 randomisation and assuming a standard deviation of 4.5 mm.
b Assuming an average baseline lesion size of 18 mm.

If the drop-out rate in any of the sub-groups are larger than 10%, the sample size of randomised subjects for that sub-group may be increased to up to 30.

The study was planned to be have a randomisation ratio of 2:1 with 2 subjects receiving quinagolide vaginal ring for each subject receiving placebo vaginal, however it was discovered, after LPLV but before database lock, that the randomisation list used during the study had a 1:1 ratio between quinagolide vaginal ring placebo vaginal ring. The use of a 1:1 ratio instead of a 2:1 ratio will increase the power to detect a difference between quinagolide vaginal ring and placebo vaginal ring.

4 Subject Disposition

4.1 Screened Subjects

Screened subjects who discontinue prior to randomisation 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 summarised for the three types of lesions combined (n and % of total number of screened subjects) by: randomised, reason for failure and all.

4.2 Subject Disposition

Subject disposition with respect to analysis sets (Safety, FAS, PP) will be summarised for each of the three types of lesion (endometrioma, DIE and adenomyosis) by treatment and in total. If applicable a row will be added to the table counting the number of subjects that are randomised but not treated.

4.3 Subject Completion/Discontinuation

Completion of treatment will be based on the study completion/early withdrawal form, attendance to end-of-treatment MRI will be based on the MRI form for visit 8, and completion of follow-up will be based in the follow-up call form.

Based on the FAS, subjects completion of treatment and attendance to follow-up MRI, will be summarised (n and %): completed and attending follow-up MRI, completed and not attending follow-up MRI, discontinued and attending follow-up MRI (with information on primary reason for discontinuation according to study completion/early withdrawal form), discontinued and not attending follow-up MRI (with information on primary reason for discontinuation according to study completion/early withdrawal form). The summaries will be performed by treatment and in total for each of the three types of lesion (endometrioma, DIE and adenomyosis) and for the three types of lesions combined. For each of these four summaries the treatment group difference in the proportion of subjects who discontinue treatment will be tested using Fishers exact test.

Based on the FAS, subjects completion of follow-up will be summarised (n and %). The summaries will be performed by treatment and in total for each of the three types of lesion (endometrioma, DIE and adenomyosis), for endometriosis (endometrioma and DIE), and for the three types of lesions combined.

4.4 Subject Disposition and Completion by Trial Site

The summaries described in section 4.2 and 4.3 will also be performed by trial site.

4.5 Time to treatment discontinuation

Based on the FAS five Kaplan-Meier plots for time to treatment discontinuation (from the study completion form) will be used to compare treatment groups. One plot for each of the three types of lesion (endometrioma, DIE, and adenomyosis), one for endometriosis (endometrioma and DIE), and one for the three types of lesions combined.

The Kaplan-Meier plots will compare the 2 treatment groups, log rank tests will be performed comparing the two treatment groups.

4.6 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 combined FAS, subject disposition with respect to analysis sets will be listed by site, treatment and subject number, this listing will include information on in which subgroup the subject was allocated to at randomisation. Subjects who discontinued from the trial will be listed by site, treatment, and subject number 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 be rated as major. Major protocol deviations will lead to exclusion of data from the per protocol (PP) analysis sets. 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 randomisation
- Non-compliance with investigational medicinal product (IMP) treatment regimen for >20% of days during the non-menstrual period. The non-menstrual period of each cycle (cycle 1 to 4) is defined as the period from stop date of menstrual bleeding (excluding the stop day) to start of menstrual bleeding (excluding the start date). For a given cycle the stop date is based on the menstrual bleeding pattern form obtained at the beginning of the cycle, and the start date of menstrual bleeding is based on the menstrual bleeding pattern form obtained at the end of the cycle. The calculation of non-compliance percent is based on the combined non-menstrual period for cycle 1 to 4. In case of missing information on start and/or stop dates, the entire cycle in question will be considered as non-menstrual.

Unforeseen deviations deemed to impact the primary endpoint of the trial may additionally be rated as major protocol deviations by the Ferring clinical team, with support from the Syneos 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 lock.

5.1 Major protocol deviations

Based on the FAS analysis sets major protocol deviations will be summarised (n and %) for each category of protocol deviation, by treatment and in total for each of the three types of lesion (endometrioma, DIE and adenomyosis), for endometriosis (endometrioma and DIE), and for the three types of lesions combined.

5.2 Listing

Based on the combined FAS 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. All major protocol deviation will also be listed separately.

6 Analysis Sets

6.1 Full Analysis Sets

For this trial five full analysis sets (FAS) will be defined. One for each of the three types of lesions, one for endometriosis (endometrioma and DIE combined) and one for all three types of lesions combined (referred to as the combined FAS).

For the analysis of endometrioma, the FAS comprises of all randomised and treated subjects with at least one endometrioma lesion ≥10 mm at baseline.

For the analysis of DIE, the FAS comprises of all randomised and treated subjects with at least one DIE lesion ≥10 mm at baseline.

For the analysis of adenomyosis, the FAS comprises of all randomised and treated subjects with a maximum junctional thickness ≥12 mm at baseline or the size of another adenomyosis lesion ≥10 mm at baseline.

For the analysis of endometriosis, the FAS comprises of all randomised and treated subjects with at least one endometrioma lesion ≥10 mm at baseline and/or at least one DIE lesion ≥10 mm at baseline (referred to as the endometriosis FAS).

For the analysis of the three types combined, the FAS comprises of all randomised and treated subjects.

Treatment assignment for summaries and analyses are according to planned treatment. The study was planned to be have a randomisation ratio of 2:1 with 2 subjects receiving quinagolide vaginal ring for each subject receiving placebo vaginal ring, however the randomisation list used during the study had a 1:1 ratio between quinagolide placebo and placebo vaginal ring. The planned treatment used in the FAS is the treatment according to the actually used randomisation list.

6.2 Per Protocol Analysis Sets

For each of the lesion types the corresponding PP analysis set comprises all subjects from the corresponding FAS except those excluded due to major protocol deviations as defined in section 5.

6.3 Safety Analysis Sets

The combined safety analysis set (SAS) comprises all treated subjects and are analysed according to the actual treatment received. If a subject receives both treatments during the trial, quinagolide treatment will be considered as the actual treatment for the safety analysis.

Four additional SAS will be defined. One for each of the three types of lesions, one for endometriosis (endometrioma and DIE).

For the analysis of endometrioma, the SAS comprises of all treated subjects with at least one endometrioma lesion ≥10 mm at baseline.

For the analysis of DIE, the SAS comprises of all treated subjects with at least one DIE lesion ≥10 mm at baseline.

For the analysis of adenomyosis, the SAS comprises of all treated subjects with a maximum junctional thickness ≥12 mm at baseline or the size of another adenomyosis lesion ≥10 mm at baseline.

For the analysis of endometriosis, the SAS comprises of all treated subjects with at least one endometrioma lesion ≥10 mm at baseline and/or at least one DIE lesion ≥10 mm at baseline (referred to as the endometriosis SAS).

7 Trial Population

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

All summaries in this section will be performed by treatment and in total for each of the three types of lesion (endometrioma, DIE and adenomyosis), for endometriosis (endometrioma and DIE), and for the three types of lesions combined. In addition, summaries of the three types of lesions combined will be performed by treatment and in total for each site. Listings will be based on the combined FAS only.

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 and body measurements (age (calculated using date of visit 1 and time of birth), race and ethnicity, height, weight and BMI) will be summarised.

7.1.2 Vital Signs at Baseline

Baseline vital signs will be summarised as described in section 10.4.

7.1.3 Endometriosis History

Endometriosis initial diagnosis (time since initial diagnosis, method, stage and anatomic location) will be summarised. In case of partial missing date of initial diagnosis, following imputation will be used: If both day and month are missing 01JAN will be used, if only the day is missing 01 will be used as the day.

Endometriosis surgical history since the initial diagnosis (Any history (yes/no), time since, method and type of surgery) will be summarised. In case of partial missing date of initial diagnosis, following imputation will be used: If both day and month are missing 01JAN will be used, if only the day is missing 01 will be used as the day.

Menstrual history and reproductive history will be summarised.

7.1.4 Endometriosis/adenomyosis lesions at baseline

The number of lesions per subject, the size the lesions and the sum of the sizes of the lesion will be summarised.

The occurrence of subjects having more than one lesion type will be summarised for the three types of lesions combined in the following way: The subjects will be categorised in the following groups: Endometrioma lesions only, DIE lesions only, adenomyosis lesions only, endometrioma and DIE lesions, endometrioma and adenomyosis lesions, DIE and adenomyosis lesions, endometrioma, DIE and adenomyosis lesions. This will be based on the occurrence of lesions ≥10 mm at the baseline MRI.

7.2 Medical History

Medical history recorded at screening visit will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0.

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

Ongoing (ongoing at time of screening) 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

Medications will be coded using the World Health Organization Drug Reference List and 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).

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 and Gynaecological Examination

The results of the physical and gynaecological examinations at baseline will be summarised.

7.5 TVU at baseline

Baseline TVU results will be summarised as described in section 9.3.3 and 10.6.

7.6 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

Unless otherwise specified all summaries in this section will be based on the FAS, and will be performed by treatment and in total for each of the three types of lesion (endometrioma, DIE and adenomyosis), for endometriosis (endometrioma and DIE), and for the three types of lesions combined.

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 Extent of Exposure

Total extent of exposure will be summarised. Total extent of exposure will be based on information from the vaginal ring administration form.

The total extent of exposure will be the date of the last ring removal minus the date of first ring insertion.

Extent of exposure for each cycle (cycle 1 to 4) will also be summarised, but only for the three types of lesions combined. Extent of exposure for each cycle will as above be calculated as the difference in ring removal dates and insertion dates.

Additionally the extent of exposure counted in cycles will be summarised as a categorical variable. A subject is considered exposed in a given cycle if a ring is inserted at visit 2, visit 5, visit 6, or visit 7 respectively.

8.2 Treatment Compliance

The treatment compliance in percent will be summarised. Treatment compliance will be based on information about missed dose from the medication errors form and the vaginal ring administration form.

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.

The expected number of days exposed to the ring is; if the subjects completes treatment, the date of visit 8 minus the date of visit 2; and if the subject discontinues treatment the date of withdrawal minus the date of visit 2. The number of days exposed to the ring is based on the vaginal ring administration form and taking information on the number of days with missed dose >24 hours from the medication errors form into account.

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

8.3 Listings

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

9 Efficacy

9.1 General Considerations

All efficacy endpoints will be summarised using descriptive statistics and will be performed by treatment and in total for each of the three types of lesion (endometrioma, DIE and adenomyosis), for endometriosis (endometrioma and DIE), and for the three types of lesions combined. 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, unless otherwise specified.

All 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".

9.2 Primary Endpoint

The primary endpoint consists of the following three evaluations, all based on the MRI examinations at baseline and at end-of-treatment:

- The changes from baseline to end-of-treatment in the sum of sizes (mm) of all endometrioma lesions ≥10 mm at baseline
- The changes from baseline to end-of-treatment in the sum of sizes (mm) of all DIE lesions ≥10 mm at baseline
- The changes from baseline to end-of-treatment in the sum of sizes (mm) of the maximum junctional thickness (if ≥ 12 mm) and all other adenomyosis lesions ≥10 mm at baseline

Based on the FAS and the PP analysis sets the absolute sum of sizes at baseline and at end-of-treatment, and the change in the sum of sizes from baseline to end-of-treatment will be summarised. The summaries will be performed by treatment and in total for each of the three types of lesions (endometrioma, DIE, and adenomyosis).

9.2.1 Primary Analyses

The primary analyses are based on the FAS.

For each type of lesion (endometrioma, DIE and adenomyosis), the primary endpoint is the change in the sum of the lesion sizes at end-of-treatment, i.e. the difference between the active treatment

group and the placebo group in the change from baseline in the sum of the lesion sizes of the same type at the end-of-treatment. The baseline is defined as the sum of the sizes of all lesions of the same type ≥10 mm obtained from the MRI examination at screening. At end-of-treatment / cycle 4, the sizes of all lesions included at baseline of the same type will be summed. For each type of lesions, subjects with at least one lesion of that type ≥10 mm at baseline will be included.

If a subject is prematurely discontinued during or after cycle 2, an end-of-treatment MRI examination will be performed. The results from this end-of-treatment MRI will be used to calculate the primary endpoints.

If the end-of-treatment MRI examination results in an assessment of a lesion size as <5 mm without a precise value (or categorised as detectable), the size of this lesion will be imputed as 2.5 mm. If the end-of-treatment MRI examination results in a lesion assessed as being truly not detectable, the size of this lesion will be imputed as 0 mm.

If the end-of-treatment MRI examination is not performed or is missing, the missing measurement will be imputed using a multiple imputation (MI) strategy. The imputation will be based on a missing a random assumption (MAR). The missing sum of lesion sizes at end-of-treatment will be imputed by regression-based imputation models using treatment group, baseline sum of lesion sizes, and the overall NRS score (at visit 2, 5, 6, 7, 8) as the predictors. The imputation procedure will be repeated 100 times. For technical reasons, the imputation is implemented in two steps as described below.

Firstly any non-monotone missingness of the predictors mentioned above is imputed using the Markov chain Monte Carlo (MCMC) method, assumptions underlying this partial imputation step are such that subjects with missing data follow the same model as other subjects with the same value of the observed predictors that have complete data, and this is a reasonable assumption for this partial imputation, because subjects tend to miss intermediate visits due to scheduling conflicts or other reasons unrelated to their medical condition under study.

Secondly all monotone missingness is imputed, using a standard MAR based MI approach for monotone missingness, which imputes variables one at a time in the following order: the overall NRS score at visit 2, at visit 5, at visit 6, at visit 7, and at visit 8, and finally the sum of lesion sizes at end-of-treatment.

For each type of lesion and each imputation, the primary endpoint will be analysed using an analysis of covariance (ANCOVA) model, with the change in the sum of lesion sizes from baseline measured at end-of-treatment as the dependent variable, the baseline sum of lesions as covariate, and the treatment group as fixed effect. The treatment difference between active treatment versus placebo will be estimated for each of the three types of lesions.

Finally, the 100 different imputations are combined to an estimate of the treatment difference between active treatment versus placebo and its 95% confidence interval and corresponding p-value using SAS Proc Mianalyze.

In order to control the overall type I error at 5%, the Hochberg procedure is implemented by ranking the 3 p-values in a decreasing order. If the largest p-value is ≤0.05, superiority is established for all 3 types of lesions. If the largest p-value is >0.05, but the middle p-value is ≤0.025, superiority is established for the two types of lesions with the smaller p-values. If the largest p-value is >0.05 and the middle p-value is >0.025, but the smallest p-value is ≤0.0125, superiority is established for only the type of the lesion with the smallest p-value. If the largest p-value is >0.05, the middle p-value is >0.025, and the smallest p-value is >0.0125, superiority is not established for any of the 3 types of lesions.

9.2.2 Sensitivity Analyses

A number of sensitivity analyses are planned to establish robustness of the primary analysis, including summary statistics (expect for the placebo based MI in section 9.2.2.2). All sensitivity analysis except the PP analysis will be performed on the FAS.

9.2.2.1 Per Protocol Analysis

To test efficacy in more perfect conditions. For each type of lesion an analysis similar to the primary analysis will be performed using the PP population.

9.2.2.2 Missing Data

For each type of lesion three sensitivity analyses will be performed to investigate the impact of missing data, two completer analyses and one MI analysis:

Firstly, an ANCOVA analysis similar to the primary analysis, but without doing any imputation, and using only data from subject that have completed the scheduled treatment and have information from both the baseline and the cycle 4 MRI.

Secondly, a similar ANCOVA without imputation, using data from all subjects that have information from both the baseline and the end-of-treatment MRI.

Thirdly, a MI analysis will be performed using MI for missing data in a placebo-based pattern mixture model (based on a missing not at random (MNAR) condition). A MNAR assumption will be used as the primary analysis gives an unbiased estimation of the treatment effect under the MAR assumption.

This is done in 3 steps firstly initiating the process by imputing any non-monotone missingness using the MCMC method, just as in the primary analysis, the non-monotone missingness (missing at intermediate visits) is assumed to be MAR opposed to missingness due to drop-out which is assumed to MNAR. That is the non-monotone missingness is assumed to be unrelated to the medical condition, whereas the monotone missingness is allowed to depend on the medical condition. Secondly all monotone missingness is imputed, an approach, which imputes variables one at a time in the following order: NRS score at visit 2, at visit 5, at visit 6, at visit 7, and at visit 8, and finally the sum of lesion sizes at end-of-treatment, similar to the primary analysis, however this imputation will be based on only the placebo group. So the mean of the imputed values will be based on the mean of the placebo subjects with the same predictors as the subject that has missing

information. Thirdly the 100 imputations are analysed and combined similarly to the primary analysis.

9.2.2.3 Actual Treatment

For each type of lesion, the primary analysis will be performed using the actual treatment rather than the planned treatment. If a subject receives both treatments, then the treatment that the subject received for the longest period is used as the actual treatment for this sensitivity analysis.

9.2.2.4 Including Small Lesions at Baseline

For each type of lesion, the primary analysis performed on a redefined outcome. The outcome will be the change from baseline to end-of-treatment in the sum of all lesions of that type including the lesions below <10 mm in size at baseline, as opposed to the primary analysis focusing on all lesion of that type that are ≥10 mm at baseline.

9.2.2.5 Adjusting for Previous Hormonal Treatment

For each type of lesion the primary analysis will be performed adjusting for previous hormonal treatment as a fixed factor. Previous hormonal treatment will be defined as a Yes/No variable and will take the value yes if the subject has any prior medication with a stop date less than 6 month prior to first us of IMP, with ATC classification 1st level equal to “Genito urinary system and sex hormones” and ATC classification 2nd level equal to “sex hormones and modulators of the genital system” or “other gynaecologicals” and the value no otherwise.

9.2.3 Additional Analyses

Based on the endometriosis FAS (endometrioma and DIE). The changes from baseline to end-of-treatment in the sum of sizes (mm) of all endometriosis (endometrioma and DIE) lesions ≥10 mm at baseline will be analysed using a similar ANCOVA model and a similar imputation scheme as the primary analysis.

9.2.4 Figures

Figures based on the FAS for each of the three types of lesion (endometrioma, DIE and adenomyosis), for endometriosis (endometrioma and DIE), and for the three types of lesions combined will be prepared. The mean of the primary outcome (with 95% confidence interval) will be graphed as a function time (Baseline and End-of-treatment) for the two treatment groups in the same figure. No imputations will be used for the figures.

9.3 Secondary and Exploratory Endpoints

The summaries and analysis of the secondary efficacy endpoints will be performed for the FAS. No sensitivity analysis will be performed for any of the secondary or exploratory outcomes.

9.3.1 Percentage of Lesion Size Changes by Type on MRI

For each type of lesion (endometrioma, DIE and adenomyosis), the percentage change in the sum of lesion sizes, will be analysed using a similar ANCOVA model and a similar imputation scheme as the primary endpoint, but both the baseline sum of sizes and the cycle 4 / end-of-treatment sum of sizes will be log transformed prior to analysis. The estimated difference between treatment groups will be back transformed to ease interpretation.

If the end-of-treatment MRI examination results in that all lesions of the same type are assessed as truly not detectable the sum will be imputed as 1 mm, in order to facilitate the log-transformation.

9.3.2 Endometrioma and DIE Changes in Volume on MRI

The absolute sum of volumes at baseline and at end-of-treatment, and the change in the sum of volumes from baseline to end-of-treatment will be summarised. The summaries will be performed by treatment and in total for each of the two types of lesions (endometrioma and for the two types combined and DIE).

For each of the two types of lesions (endometrioma and DIE) and for the two types combined, the change in the sum of lesion volumes, will be analysed using a similar ANCOVA model and a similar imputation scheme as the primary endpoint.

9.3.3 Endometrioma Size Changes by TVU

The absolute sum of sizes of endometrioma lesions assessed by TVU at baseline and at end-of-treatment, and the change in the sum of sizes from baseline to end-of-treatment will be summarised. The summaries will be performed by treatment and in total only for endometrioma lesions.

The change in the sum of lesion sizes assessed by TVU, will be analysed using a similar ANCOVA model and a similar imputation scheme as in the primary endpoint.

9.3.4 Other Secondary and Exploratory Endpoints

All summaries in this section will be performed by treatment and in total. As indicated in Table 9-1 some endpoints will be summarised and analysed for each of the three types of lesion (endometrioma, DIE and adenomyosis) and for endometriosis (endometrioma and DIE), some for all types of lesion combined, and some for both.

No imputation will be done for the analysis of these other secondary and exploratory endpoints. The endpoint derived from the MRI will, however, use the end-of-treatment assessment even if the end-of-treatment assessment is performed before end of cycle 4.

Table 9-1 Analyses of Other Secondary and Exploratory Endpoints

Endpoint	Analysis method					Presentation	
	ANCOVA	Repeated measures ANCOVA	Logistic regression	Negative Binomial regression	Proportional odds	By type of lesion and disease	All types of lesions combined
Proportion of lesions by type with a decrease in a size of ≥5 mm on MR images at cycle 4			X			X	
Proportion of subjects with a lesion of any type decreased in a size of ≥5 mm on MR images at cycle 4			X				X
Number of new endometrioma, DIE and adenomyosis lesions by type on MR images at cycle 4				X		X	
Number of disappearing endometrioma, DIE and adenomyosis lesions by type on MR images at cycle 4				X		X	
Changes in the total physical sign pain score and change in the total symptom and sign severity score of the Biberoglu and Behrman (B&B) scale at cycle 4	X					X	X
Changes in the Numerical Rating Scale (NRS) pain scores at cycles 1, 2, 3 and 4		X				X	X
Changes in each of the five EHP-30 scores and the total EHP-30 score per cycle at cycles 2 and 4		X				X	X
Changes in the menstrual bleeding pattern over 4 cycles		X			X	X	X
Change in serum levels of prolactin, TSH, IGF-1 during cycle 1, at cycles 2 and 4		X				X	X
Changes in the sizes of uterine fibroids on MR images at cycle 4	X						
Changes in the sizes of uterine fibroids assessed by TVU at cycle 4	X						
Changes in circulating levels of VEGF, PlGF, IL-6, CA125 and sFlt-1 at cycle 4	X					X	X

Note: Exploratory endpoints are shaded in grey.

9.3.4.1 Binary Endpoints

Secondary endpoints related to proportion of lesions with a decrease in a size of ≥5 mm at cycle 4 and proportion of subjects with a lesion of any type that decreased in a size of ≥5 mm at cycle 4 will be based on all lesions ≥10 mm at baseline.

The proportion of lesions with a decrease as defined above and the proportions of subjects with at least one lesion decreased as defined above will be summarised

The proportion of lesions will be analysed using logistic regression for binary data with logit link function, the generalised estimating equation (GEE) approach will be used to account for correlated data (multiple lesions in one subject), and the analysis will be adjusted for baseline lesion size. The analyses will be performed for each of the three types of lesions, and for endometriosis (endometrioma and DIE).

The proportion of subjects will be analysed using logistic regression for binary data with logit link function, and the analysis will be adjusted for the number of lesions ≥10 mm at baseline. The analyses will be performed for the three types of lesions combined.

Menstrual bleeding pattern will be analysed by looking at the first occurrence of change from baseline (visit 2) in the amount of menstrual flow (either to a more heavy flow or to a more mild flow). This will be analysed using the proportional odds regression model. The analyses will be performed for each of the three types of lesions, and for endometriosis (endometrioma and DIE).

The treatment differences between active treatment versus placebo will be reported as odds ratios with 95% confidence intervals and corresponding p-values for each of these endpoints.

9.3.4.2 **Count Data**

The number of new lesions of each of the three types of lesions will be counted for all subject, regardless of which types of lesions the subject had at baseline. The definition of a new lesion is a lesion that is > 0 mm at the end-of-treatment MRI, but was non-detectable at baseline.

The number of disappearing lesions of each of the three types of lesions will be counted for all subject with at least one lesion of that type that is > 0 mm at baseline. The definition of a disappearing lesion is a lesion that is detectable at baseline, but is non-detectable at end-of-treatment.

The number of new and disappearing lesions will, for each type of lesion, be summarised as categorical variables.

The analysis of the number of new lesions will be performed for each of the three types of lesion and for endometriosis (endometrioma and DIE). It will be analysed using a negative-binomial regression with log link function.

The analysis of the number of disappearing lesions will be performed for each of the three types of lesion and for endometriosis (endometrioma and DIE). It will be analysed using a negative-binomial regression with log link function, using the number of lesions of that type as off-set.

The treatment differences between active treatment versus placebo will be reported as rate ratios with 95% confidence intervals and corresponding p-values for each of these endpoints.

9.3.4.3 Continuous Endpoints

The analysis of the secondary endpoints related to PROs (B&B, NRS, and EHP-30), endocrine parameters (prolactin, TSH, and IGF-1), serum endometriosis biomarkers (VEGF, PlGF, IL-6, CA125, and sFlt-1), sizes of uterine fibroids (the sum of the size of all fibroids) assessed by MRI and TVU, will be described in this subsection.

The absolute value at baseline and the absolute value at each post baseline measurement, and the change from baseline to each post baseline measurement will be summarised. These endpoints will be analysed using a repeated measures ANCOVA model, with the change from baseline at each post-baseline time point as the dependent variable, the baseline value as a covariate, and the treatment group and treatment group by time as fixed effects. The error-covariance matrix will be unstructured. For the endpoints only measured once post baseline, an ordinary ANCOVA similar to the one used in the primary analysis will be applied (without imputations). The analyses will be performed for each of the three types of lesions, and for endometriosis (endometrioma and DIE). The treatment difference between active treatment versus placebo will be reported with 95% confidence interval and corresponding p-value for each post baseline of these endpoints.

As an additional analysis the menstrual bleeding pattern will be investigated by analysing the number days with menstrual bleeding (calculated as the stop date of menstrual bleeding minus start day plus 1) for each of the four cycles under treatment and the length of the menstrual cycle (calculated as the difference between two consecutive start of menstrual bleeding dates) for each of the four cycles under treatment. The baseline values for these two variables will be the number of bleeding days and the length of the menstrual period of the last pre-treatment cycle, respectively. If the stop date of a menstrual bleeding is missing due to the subject still bleeding at the RM+7 visit, the visit date plus 1 is used for calculating the length of the bleeding period. If the start date of menstrual bleeding is missing due to the subject having delayed or skipped menstrual bleeding, both of the two length of menstrual cycles will be considered missing, and the length of the bleeding period will be set to 0. To summarise the occurrence of delayed or skipped menstrual bleeding descriptive tables summarising the number of delayed or skipped menstrual bleedings and the number of subjects that experience at least one delayed or skipped menstrual bleeding will be prepared.

9.4 Pharmacokinetics

Plasma concentration of quinagolide and its metabolites will be analysed descriptively, by summarising (N, mean (SD), geometric mean (CV%), min, and max) by visit, for all subjects that received active quinagolide. A population pharmacokinetic 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.

9.5 MRI-derived Imaging Biomarkers

The exploratory endpoints related to the MRI-derived perfusion and diffusion imaging biomarkers will be analysed by the central imaging laboratory and will be reported separately

9.6 Listings

All observed endpoints will be listed by site, treatment, and subject number. For the laboratory endpoints values outside the reference range (with information on clinically significance) and markedly abnormal values will be flagged.

10 Safety

10.1 General Considerations

Safety parameters will be evaluated for the combined safety analysis data set for all types of lesions combined, for each of the three types of lesions separately, and for endometriosis (endometrioma and DIE), See section 6.3 for the definition of the safety analysis sets. All summaries will be performed by treatment. For adverse events (AE) the following rules will apply:

Treatment period	AE to be included
Pre-treatment period	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
Treatment emergent AE	A treatment-emergent adverse event is any adverse event occurring after start of IMP and before the follow-up phone call, or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after start of IMP and before the follow-up phone call.

For safety data where only a partial date has been reported, the following rules will be applied:

- Year and month given: for start dates, starting first day in the month and for stop dates, stopped last day in the month
- Only year given: for start dates, starting 1st of January and for stop dates, stopped 31st of December

10.2 Adverse Events

AEs are classified according to MedDRA version 21.0.

An AE which occurs between signing informed consent and the first dose of the IMP or a pre-existing condition that worsens in intensity after signing of informed consent is defined as a pre-treatment AE. A treatment-emergent adverse event is any adverse event occurring after start of IMP and before the follow-up phone call, or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after start of IMP and before the follow-up phone call. If the timing of an AE cannot be established in relation to the administration of IMP, it will be considered as a treatment emergent AE. Pre-treatment AEs will be presented in a separate data listing only. AE in connection with screening safety lab values are considered pre-treatment if the blood is sampled prior to treatment.

If causality for an AE is missing then the AE will be considered related. If intensity for an AE is missing then the AE will be considered severe. If seriousness for an AE is missing then the AE will be considered serious. If outcome for an AE is missing then the AE will be considered not recovered.

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 by intensity
- All adverse drug reactions (ADR) (i.e. an AE judged by the investigator and/or sponsor to have a reasonable possible causality to the IMP)
- ADR by intensity
- TEAEs leading to death
- Serious TEAEs
- Serious ADR
- TEAEs leading to discontinuations
- ADR leading to discontinuations

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 TEAEs
- Mild TEAE
- Moderate TEAE
- Severe TEAE
- All ADR
- Mild ADR
- Moderate ADR
- Severe ADR
- Treatment emergent unrelated adverse events
- TEAEs leading to death

- ADRs leading to death
- Serious TEAE
- Serious ADR
- Non- serious ADR
- TEAEs leading to discontinuation
- ADRs leading to discontinuation
- TEAEs for impulse control disorder search string (see appendix 2)
- ADRs for impulse control disorder search string (see appendix 2)
- TEAEs with an incidence ≥5% of subjects in any treatment group
- Non-serious TEAEs with an incidence ≥5% of subjects in any treatment group

Supporting data listings will be provided for all adverse events sorted by centre and subject number and date of onset. Further, data listings by MedDRA SOC sorted alphabetically and Preferred Term sorted in decreasing frequency of occurrence will be provided for:

- All TEAE
- Severe TEAE
- Serious TEAE
- TEAE leading to death
- TEAE leading to discontinuation
- Treatment emergent adverse events to be followed up after end-of-trial

10.3 Safety Laboratory Variables

Safety lab values are planned to be measured twice, at baseline (visit 1), at end-of-treatment (visit 8). If multiple blood samples are obtained prior to first dose of IMP the last blood sampling performed prior to the first dose of IMP is used as baseline.

Laboratory variables will be grouped under “Haematology” and “Clinical Chemistry”.

10.3.1 Summary Statistics

Mean change and mean percentage (%) change from baseline at end-of-treatment 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 both baseline and end-of-treatment as well as for changes from baseline to end-of-treatment (both absolute change and relative change).

10.3.2 Laboratory Variable Changes Relative to Normal Range

Changes relative to normal ranges are presented with shift tables with total number of subjects, and number and percent of subjects who experienced a shift from baseline to end-of-treatment. The laboratory reference ranges are provided by the central laboratory. The following categories for shift tables are defined:

- Low: Values which are below the lower reference range limit;
- Normal: Values which are within the lower and upper reference range;
- High: Values which are above the upper reference range limit.

For all haematology and clinical chemistry variables, shift tables will be prepared to compare baseline values to the end-of-treatment value. More specifically, for haematology and clinical chemistry, tables presenting the changes from *Low* or *Normal* to *High* and from *High* or *Normal* to *Low* will be provided.

10.3.3 Markedly Abnormal Changes

For each laboratory variable, a summary tables will be prepared displaying the number and percentage of subjects in each treatment group with normal baseline values but having at least one pre-specified markedly abnormal value any time after first dose of IMP. Pre-specified markedly abnormal criteria for laboratory tests are given in Appendix 1.

10.3.4 Data Listings

All laboratory values will be listed by subject number and time point. Values outside the reference range (with information on clinically significance) and markedly abnormal values will be flagged.

10.4 Vital Signs

Vital signs (pulse rate, systolic blood pressure, and diastolic blood pressure) are planned to be measured 4 times during the trial, at visit 1, at visit 2 prior to first dose of IMP, at visit 3 and at end-of-treatment (visit 8), for each of the 4 visits vital signs will be measured 4 times; in supine position, in seated position, at 1 minute after standing, and at 3 minutes after standing. For each visit changes in systolic and diastolic blood pressure will be calculated using the minimum standing measurement minus the seated measurement and the minimum standing measurement minus the supine measurement. Baseline for all vital signs analyses will be the values obtained at the last assessment prior to the first dose of IMP.

10.4.1 Summary Statistics

Mean change and mean percentage (%) change from baseline to visit 3 and to end-of-treatment will be presented for each vital signs variable (including change from sitting to standing and from supine

to standing as described above). In addition, descriptive statistics, i.e., the number of subjects with data, mean (standard deviation), median, minimum, and maximum values, will be presented for the observed values (at screening, at baseline, at visit 3, and at end-of treatment) and for change from baseline (both absolute change and relative change) to visit 3 and at end-of-treatment for each vital signs variable(including change from sitting to standing and from supine to standing as described above).

10.4.2 Markedly Abnormal Changes

Summary tables will be prepared displaying the number and percentage of subjects with normal baselines who had one or more pre-specified markedly abnormal treatment-emergent values, according to the definition in Appendix 1.

10.4.3 Data Listings

All vital signs values (including change from sitting to standing and from supine to standing as described above) will be listed by subject number and time point. Markedly abnormal values and clinically significant changes or values will be flagged.

10.5 Physical and gynaecological examinations

Physical and gynaecological examinations are planned at baseline and at end-of-treatment. At the physical examination a number of body systems will be assessed, and at gynaecological examination a number of categories will be assessed. Each resulting in a result of normal, not clinically significant abnormal, or clinically significant abnormal. If multiple examinations are performed after first dose of IMP, then at worst case approach will be used for reporting, such that if any post baseline examination are judged as clinically significant abnormal, this result will be used as the end-of treatment value, and only if all post baseline examinations are judged as normal the end-of-treatment value will be normal.

10.5.1 Summary Statistics

Shift tables summarising the number (%) of subjects that shifted between all combinations of baseline and end-of-treatment values for each body system examined at the physical examination and each category examined at the gynaecological examination will be produced. The number of subjects with baseline values will be used as denominator when percentages are calculated (e.g. the percentage of subjects going from normal to not clinically significant abnormal will be using the number of subjects being normal at baseline as denominator).

10.5.2 Data listings

All subjects with any abnormalities at any visit will be listed with all physical and gynaecological examination evaluations.

10.6 TVU

TVU is planned at baseline and at end-of-treatment. The overall interpretation of TVU results in a result of normal, not clinically significant abnormal, or clinically significant abnormal. If multiple examinations are performed after first dose of IMP, then a worst case approach will be used for reporting, such that if any post baseline examination are judged as clinical significant abnormal, this result will be used as the end-of treatment value, and only if all post baseline examinations are judged as normal the end-of-treatment value will be normal.

10.6.1 Summary Statistics

Shift tables summarising the number (%) of subjects that shifted between all combinations of baseline and end-of-treatment values for the overall interpretation will be produced. The number of subjects with that baseline values will be used as denominator when percentages are calculated (e.g. the percentage of subjects going from normal to not clinically significant abnormal will be using the number of subjects being normal at baseline as denominator).

The number of subjects with ovarian cyst will be summarised at baseline and at end-of-treatment.

The endometrial thickness at baseline, at end-of-treatment and the change from baseline to end-of-treatment will be summaries by time point.

10.6.2 Data listings

All subjects with any abnormalities at any visit and/or any ovarian cyst at any visit will be listed with all TVU evaluations.

11 Interim Analyses

No interim analysis is planned for this trial.

12 Deviations from Protocol Analysis

The Study Protocol stated that the primary analysis should be adjusted for site. In this SAP the primary analysis is not adjusted for site, this change has been made because of the actual distribution of subjects on sites. We have 4 out of 6 sites with 4 or less subjects. Adjustment for site leads to a high risk of noninformative sites.

The study was planned to be have a randomisation ratio of 2:1 with 2 subjects receiving quinagolide for each subject receiving placebo, however it was discovered, after LPLV and before database lock, that the randomisation list used during the study had a 1:1 ratio between quinagolide placebo. The use of a 1:1 ratio instead of a 2:1 ratio will increase the power to detect a difference between quinagolide vaginal ring and placebo vaginal ring.

The use of the 1:1 randomization ratio, have not led to any change of the planned analysis in this SAP.

13 References

[1] Bragheto A, Caserta N, Bahamondes L, Petta CA. Effectiveness of the levonorgestrel-releasing intrauterine system in the treatment of adenomyosis diagnosed and monitored by magnetic resonance imaging. Contraception 2007; 76: 195-199

[2] Rubin, D. B. (1987). Multiple Imputation for Nonresponse in Surveys. New York, John Wiley and sons.

Appendix 1 Markedly Abnormal Laboratory Safety Values, Vital Signs and ECGs

Table 1: Markedly abnormal Criteria for Laboratory Tests

Variable	Units	Markedly abnormal Criteria	
		Low	**High**
Haematology			
Haemoglobin	g/L	≤ 80	Not applicable
Haematocrit	Ratio	>0.20	>0.60
Total WBC	10^9/L	<2.0	>35.0
Platelets	10^9/L	<50	>999
Total RBC	10^{12}/L		Not applicable
Clinical Chemistry			
AST	IU/L	Not applicable	> 155
ALT	IU/L	Not applicable	> 165
Alkaline phosphatase	IU/L	Not applicable	> 520
GGT	IU/L	Not applicable	> 180
Total bilirubin	µmol/L	Not applicable	≥ 1.5xULN
Creatinine	µmol/L	Not applicable	>252
Albumin	g/L	<20	
Sodium	mmol/L	≤ 130	≥ 155
Potassium	mmol/L	≤ 3.0	>6.0
Phosphorus	mmol/L	>0.65	
Calcium	mmol/L	<1.75	>3.13
Glucose	mmol/L		>13.9
Total cholesterol	mmol/L	Not applicable	>10.36

Table 2: Markedly abnormal Criteria for Vital Signs*

Variable	Criterion Value	Change from Baseline
Systolic blood pressure	≥ 180 mmHg ≤ 90 mmHg A drop of 20 mmHg from changing position	Increase of ≥ 20 mmHg Decrease of ≥ 20 mmHg
Diastolic blood pressure	≥ 105 mmHg ≤ 50 mmHg A drop of 10 mmHg from changing position	Increase of ≥ 15 mmHg Decrease of ≥ 15 mmHg
Pulse rate	≥ 120 bpm ≤ 50 bpm	Increase of ≥ 15 bpm Decrease of ≥ 15 bpm
Body weight	None	Increase of ≥ 7% Decrease of ≥ 7%
Body temperature	≥ 38.3° C	Increase to ≥ 39.4°C

* To be identified as markedly abnormal, a treatment value must meet the criterion value and also the specified change from baseline.

Table 3: Abnormal Criteria for Quantitative ECG Data

Variable	Baseline	Abnormal Treatment-Emergent Value
ECG heart rate	Normal	≤ 50 bpm and decrease from baseline of ≥ 15 bpm ≥ 120 bpm and increase from baseline of ≥ 15 bpm
Duration of PR interval	Normal	≥ 220 msec
Duration of QRS interval	Normal	≥ 120 msec
Duration of QTc interval	Normal	≥ 450 msec
Duration of QTc interval	Normal	≥ 480 msec
Duration of QTc interval	Normal	≥ 500 msec
Duration of QTc interval*	Not applicable	Increase from baseline of ≥ 30 msec
Duration of QTc interval	Not applicable	Increase from baseline of ≥ 60 msec

* QTc will be calculated both using Bazett's and Fridericia's correction formulae.

Appendix 2 Impulse Control Disorder Search String

The adverse events summary table for all AEs for impulse control disorder search string mentioned in section 10.2.2 of this SAP will include all AEs with the below mentioned preferred terms.

All preferred terms under the SMQ hostility/aggression (broad) that is:

Aggression
Amygdalotomy
Anger
Antisocial behaviour
Antisocial personality disorder
Belligerence
Borderline personality disorder
Child abuse
Conduct disorder
Defiant behaviour
Homicidal ideation
Homicide
Hostility
Incest
Intermittent explosive disorder
Physical abuse
Physical assault
Psychopathic personality
Sexual abuse
Violence-related symptom
Abnormal behaviour
Activation syndrome
Affect lability
Agitated depression
Agitation
Agitation postoperative
Asphyxia
Attention-seeking behaviour
Bipolar disorder
Bipolar I disorder
Bipolar II disorder
Bite
Delinquency
Delusional disorder, jealous type
Delusional disorder, persecutory type
Disinhibition
Disruptive mood dysregulation disorder
Disturbance in social behaviour
Drowning

Elder abuse
Fight in school
Gun shot wound
Hanging
Human bite
Hypomania
Impatience
Imprisonment
Imprisonment of relative
Impulse-control disorder
Impulsive behaviour
Injury
Irritability
Irritability postvaccinal
Jealous delusion
Laceration
Mania
Oppositional defiant disorder
Paedophilia
Paranoia
Paranoid personality disorder
Paraphilia
Personality change
Personality disorder
Psychological abuse
Psychomotor hyperactivity
Psychotic behaviour
Psychotic disorder
Pyromania
Sadism
Screaming
Spousal abuse
Stab wound
Substance-induced psychotic disorder
Spousal abuse
Stab wound
Substance-induced psychotic disorder
Theft
Verbal abuse

And additionally, the following preferred terms:

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