Cover page for Protocol

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	12 November 2019

CLINICAL TRIAL PROTOCOL

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

Quinagolide Vaginal Ring on Lesion Reduction Assessed by MRI in Women with Endometriosis/Adenomyosis
(QLARITY)

EudraCT Number:	2018-000915-26
Investigational Medicinal Product:	FE 999051, Quinagolide Vaginal Ring
Indication:	Endometriosis
Phase:	2
Name and Address of Sponsor:	Ferring Pharmaceuticals A/S Global Clinical R&D International PharmaScience Center Kay Fiskers Plads 11 2300 Copenhagen S Denmark [redacted]
GCP Statement:	This trial will be performed in compliance with GCP.

SYNOPSIS

TITLE OF TRIAL

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

SIGNATORY INVESTIGATOR

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TRIAL SITES

Approximately 8-12 sites in Europe

PLANNED TRIAL PERIOD		CLINICAL PHASE
First patient first visit (FPFV)	Q3 2019	2
Last patient last visit (LPLV)	Q2 2021	

OBJECTIVES

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)

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

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

ENDPOINTS

Primary Endpoint

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

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

Exploratory Endpoints

- Changes in the MRI-derived perfusion imaging biomarkers of AUC, K^{trans}, k_{ep}, v_e, v_p at cycle 4
- Changes in the MRI-derived diffusion imaging biomarkers of ADC, D, D* and f at cycle 4
- Changes in the sizes of uterine fibroids on MR images at cycle 4
- Changes in the sizes of uterine fibroids assessed by TVU at cycle 4
- Changes in circulating levels of 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

METHODOLOGY

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.

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 (approximately 4 months) and including a wash-out period (only applicable to subjects using some hormonal products) 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 return of menses, 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 a 2:1 ratio to receive quinagolide vaginal ring or placebo vaginal ring for four menstrual cycles (cycles 1, 2, 3 and 4). 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.

Transvaginal ultrasound 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 randomisation 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.

A follow-up 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.

NUMBER OF SUBJECTS

It is estimated that 100 subjects will be screened to randomise 72 subjects in this trial, with approximately 24 subjects in each sub-group.

CRITERIA FOR INCLUSION / EXCLUSION

Inclusion Criteria

1. Informed consent signed and dated prior to any trial-related procedures.
2. In good physical and mental health to participate in the trial.
3. Pre-menopausal females between the ages of 18-45 years (both inclusive) at the time of signing the informed consent.
4. A menstrual cycle of 24-35 days (both inclusive) based on observation made in the absence

of drugs that can affect the cycle length (e.g. oral contraceptives) prior to the screening visit.

5. Body mass index (BMI) of 18-35 kg/m^2 (both inclusive) at screening.
6. Confirmation of deep infiltrating endometriosis (DIE) (lesion size ≥15 mm), endometrioma (≥20 mm) or adenomyosis (maximum junctional zone thickness ≥12 mm or focal lesion ≥15 mm) by high-resolution MRI at screening.
7. Transvaginal ultrasound documenting a uterus with no abnormalities of endometrium and presence of at least one ovary with no clinically significant abnormalities at screening. Note that presence of uterine fibroids are not exclusionary but presence of any submucosal fibroids or polyps are exclusionary.
8. Willing and able to use a non-hormonal single-barrier method (i.e. condom) for contraception from the start of screening to the end-of-treatment. This is not required if adequate contraception is achieved by vasectomy of the male sexual partner, surgical sterilisation (e.g. tubal ligation and blockage methods such as ESSURE) of the subject, or true abstinence of the subject (sporadic sexual intercourse with men requiring condom use).
9. Willing to avoid the use of vaginal douches or any other intravaginally administered medications or devices (except for tampons) from randomisation to the end of treatment.
10. Documentation of normal cervical cytology or negative human papilloma virus (HPV) results for high-risk viral subtypes upon presence of atypical squamous cells of undetermined significance, based on test(s) performed within 24 months of randomisation.
11. Willing and able to comply with trial procedures, including attending scheduled visits and adherence to treatment plan.

Exclusion Criteria

1. Use of depot medroxyprogesterone acetate (MPA) within 10 months prior to the screening visit.
2. Use of gonadotropin-releasing (GnRH) agonists (3-month depot) or dopamine agonists within 6 months prior to the screening visit.
3. Use of GnRH agonists (1-month depot or nasal spray), GnRH antagonists, aromatase inhibitors, danazol, birth control implants (e.g. NEXPLANON), progestogen or levonorgestrel-releasing intrauterine device (IUD) within 3 months prior to the screening visit.
4. Use of hormonal contraceptives (including combined oral contraceptive pill, transdermal patch, and contraceptive ring) and copper IUDs within 1 menstrual cycle prior to the screening visit.
5. Undiagnosed abnormal vaginal bleeding within the last 3 months of the screening visit.
6. History of recurrent bacterial, fungal or viral vaginal infection (i.e. ≥4 episodes within a year).
7. History of malignancy within 5 years prior to the screening visit, except for adequately managed basal cell carcinoma and squamous cell carcinoma of the skin.
8. History of orthostatic hypotension or recurrent syncope.
9. History of mental illness including occurrence of acute psychosis, bipolar disorder and schizophrenia (except for well-controlled mild or moderate anxiety and/or depression with no changes to interventions for 3 months prior to the screening visit).

10. History of sudden sleep onset episodes.
11. Known diagnosis of impulse control disorders including pathological gambling, compulsive buying, hypersexuality, and binge eating.
12. Known positive results of Human Immunodeficiency Virus (HIV) antibody tests.
13. Any other incidental, clinically significant abnormal findings than endometriotic / adenomyotic lesions identified at the screening MRI examination (e.g. suspected tumour).
14. Any clinically significant abnormal findings from vital signs, blood tests of haematology and clinical chemistry at screening, including alanine aminotransferase (ALT) >2.5 times upper limit of normal (ULN) or bilirubin >1.5 times ULN or creatinine >1.5 times ULN.
15. Any clinically significant abnormal findings at physical examination at screening.
16. Any vaginal or vulvar lesions that would interfere with vaginal ring usage.
17. Current pregnancy as confirmed by a positive serum pregnancy test at screening or planning a pregnancy within the duration of the trial, or currently breast-feeding or less than 6 months post-partum prior to the screening visit.
18. Planned surgical treatment of endometriosis or adenomyosis during the duration of the trial.
19. Continuous use of strong opioids (e.g. morphine) and/or illicit drugs (e.g. marijuana and amphetamine) for more than 2 weeks within 6 months prior to the screening visit.
20. Alcohol abuse (>14 units of alcohol a week) within 2 years prior to the screening visit.
21. Previous or current participation in a clinical trial involving a non-registered investigational medicinal product within 1 month of screening. If the trial involves a hormonal drug, the exclusion criteria 1-4 shall apply.
22. Contraindications to MRI such as having internal/external metallic devices and/or accessories (e.g. cardiac pacemakers and leg braces).
23. Hypersensitivity to any active ingredients, excipients or other components of medicinal products used in the trial, including quinagolide vaginal ring, placebo vaginal ring and any products used for MRI examination.

MEDICINAL PRODUCTS

Quinagolide vaginal ring is an extended-release system with a dose load of quinagolide 1080 µg at a target daily release rate of quinagolide 13.5 µg for up to 35 days duration.

- Quinagolide vaginal ring dose load 1080 µg at a target daily release of quinagolide 13.5 µg : administered once per menstrual cycle (up to 35 days), sequentially for 4 menstrual cycles
- Placebo vaginal ring: administered once per menstrual cycle (up to 35 days), sequentially for 4 menstrual cycles

DURATION OF TREATMENT

Subjects will be exposed to quinagolide vaginal ring or placebo vaginal ring for a maximum of four menstrual cycles.

STATISTICAL METHODS

The primary objective of this trial is to evaluate the effect of quinagolide vaginal ring on reduction of three different types of lesions, i.e. endometrioma, DIE and adenomyosis. For each type of

lesion, the primary endpoint is the change in the sum of the lesion sizes after 4 menstrual cycles.

The primary analyses will be based on all lesions with a size ≥10 mm at baseline. For each type of lesion, 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 cycle 4 as the dependent variable, the baseline sum of lesions as covariate, the treatment group and site as fixed effect. The treatment difference between the active treatment versus placebo will be reported with 95% confidence interval and corresponding p-value for each of the three lesion types. The Hochberg procedure will be used to adjust the three primary analyses for multiplicity.

The primary analyses will be based on the full analysis set, including all treated subjects as randomised. If a subject has prematurely discontinued from the trial without an end-of-treatment MRI, the missing measurement will be imputed using a multiple imputation strategy. Sensitivity analyses, including a completer analysis and an analysis of both measurable and non-measurable lesions, will be performed.

Continuous secondary efficacy endpoints, for which a baseline measurement is available, will be analysed in a similar manner as the primary endpoint or using a repeated measure ANCOVA. Percentage of changes in lesion sizes will be analysed using a similar ANCOVA model log transforming both the dependent variable and the baseline measurement. Continuous secondary efficacy endpoints where no baseline measurement is available will be analysed using an ANCOVA model. Count data will be analysed using negative binomial regression. Binary endpoints will be analysed using logistic regression or proportional regression. Safety endpoints will be summarised using descriptive statistics.

Sample size calculation
Randomisation will be performed in a 2:1 ratio to quinagolide or placebo vaginal ring. The sample size calculation is based on the primary endpoint, assuming an equal magnitude of treatment effect for all three types of lesions. For example, for adenomyosis, by assuming a baseline lesion of 18 mm and a standard deviation of 4.5 mm, 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. Similar assumptions are 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. If the drop-out rate in any of the sub-group is larger than 10%, the sample size of randomised subjects may be increased to up to 30 for that sub-group.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

List of Abbreviations

2D	2-dimension(al)
3D	3-dimension(al)
3T	3-tesla
5-HT2B	5-hydroxytryptamin 2B receptor
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical classification system
βhCG	beta unit of human chorionic gonadotropin
B&B	Biberoglu and Behrman
BMI	body mass index
CA125	cancer antigen 125
CRO	contract research organisation
d	day(s)
DCE	dynamic, contrast-enhanced
DIE	deep infiltrating endometriosis
DW	diffusion weighted
e-CRF	electronic case report form
EHP-30	Endometriosis Health Profile-30
EOT	end-of-treatment
EU	European Union
EudraCT	European Union Clinical Trial Database
FAS	full analysis set
FPFV	first patient first visit
FSE	fast spin echo
GCP	Good Clinical Practice
Gd	gadolinium
GEE	generalised estimating equation
GMP	Good Manufacturing Practice
GnRH	gonadotropin-releasing hormone
GRE	gradient echo
HIV	human immunodeficiency virus
HPV	human papilloma virus
i	insertion
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IGF-1	insulin-like growth factor-1
IL-6	interleukin 6
IMP	investigational medicinal product

IRT	Interactive Response Technology
IUD	intrauterine device
IVIM	intra-voxel incoherent motion
LATEGd	late gadolinium enhancement acquisition
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
mens. pattern	menstrual bleeding pattern
mm	millimetre
MPA	medroxyprogesterone acetate
MRI	magnetic resonance imaging
MS	multi-slice
ms	millisecond
NRS	Numerical Rating Scale
PK	pharmacokinetic(s)
PlGF	placental growth factor
PP	per protocol
PRO	patient reported outcome
r	removal
RECIST	Response Evaluation Criteria in Solid Tumours
RM	return of menses
RM+6-10	6-10 days after return of menses
RM+7	day 7 after return of menses
s	second
SAE	serious adverse event
SAP	statistical analysis plan
SE	standard error
sFlt-1	soluble fms-like tyrosine kinase 1
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TSH	thyroid-stimulating hormone
TVU	transvaginal ultrasound
ULN	upper limit of normal
V	visit
VEGF	vascular endothelial growth factor
VFA	variable flip angle
βhCG	beta unit of human chorionic gonadotropin
µg	microgram

Definition of Terms

Definitions of pharmacokinetic parameters

AUC	area under curve
C_{max}	maximum concentration
T_{max}	time to maximum concentration

Definitions (units) of MRI-derived perfusion imaging biomarkers

AUC	area under curve ($mmol \cdot kg^{-1} \cdot s$)
k_{ep}	rate constant (min^{-1})
K^{trans}	transfer constant rate (min^{-1})
v_e	fractional volume of the extravascular-extracellular space (%)
v_p	fractional volume of the plasma space (%)

Definitions (units) of MRI-derived diffusion imaging biomarkers

ADC	apparent diffusion coefficient (mm^2/s)
D	pure diffusion coefficient of cellular component (mm^2/s)
D*	pseudo-perfusion coefficient of vascular component (mm^2/s)
f	vascular fraction coefficient (%)

1 INTRODUCTION

1.1 Background

Endometriosis is an estrogen-dependent disease, pathologically characterised by the presence of endometrial-like tissue abnormally implanted outside the uterus and primarily located on the pelvic peritoneum, ovaries, and rectovaginal septum.[1] By anatomical locations of the lesions, there are three sub-types of endometriosis, i.e. superficial peritoneal endometriosis, endometrioma (or ovarian endometriosis) and deep infiltrating endometriosis (DIE, defined by the invasion of endometriotic lesions >5 mm beneath the peritoneal surface).[2,3] Endometriosis is estimated to affect 6% to 10% of women of reproductive age and clinical symptoms include pain and infertility.[4,5] It has been estimated that, in Europe, the average annual direct health care costs of endometriosis are €3113 per woman suffering from endometriosis-associated symptoms, and the indirect costs of productivity loss are twice as much as the direct health care costs.[6]

Adenomyosis, also known as endometriosis interna, is defined as benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus, which microscopically exhibits ectopic, endometrial glands and stroma.[7,8] Adenomyosis and endometriosis are considered similar diseases and are often coexisting, because both diseases are characterised by the presence of endometrial glands and stroma outside their normal locations and share a common pathophysiology of tissue changes.[9]

Surgical confirmation of endometriosis and adenomyosis through e.g. laparoscopy / hysterectomy is the gold standard of diagnosis. However, the invasive nature of surgery often leads to a delay in diagnosis of up to 10 years.[6] As a non-invasive diagnostic tool, high-resolution magnetic resonance imaging (MRI) is very useful in mapping endometriosis and preoperative surgical planning by providing information on the sub-peritoneal extent that can be overseen by laparoscopy. In general, the MRI sensitivity and specificity for the identification of endometriosis are relatively high (71% and 82%, respectively) and are sometimes even higher for endometrioma and DIE, the two sub-types of endometriosis selected in this trial.[10] Similarly, MRI is highly predictive of adenomyosis.[11] In addition, MRI can provide valuable information on tissue characterisation.

Treatment of endometriosis and adenomyosis currently involves repeated courses of medical therapy, surgical therapy, or both. Empirical treatment with analgesics and combined oral contraceptives to relieve dysmenorrhea, without prior definitive diagnosis by surgery, is usually the first line treatment especially in adolescents.[12] All established hormonal therapies (progestogen, gonadotropin-releasing hormone (GnRH) agonists, and danazol) are similarly effective. However, some of these drugs are associated with anti-ovulatory effect leading to amenorrhea and oligomenorrhea or associated with hypoestrogenic effect such as bone loss and vasomotor symptoms, all of which limit their duration of use and result in undesirable iatrogenic sterility in women seeking conception.[13,14] Long-term treatment of endometriosis or adenomyosis without undesirable anti-ovulatory or hypoestrogenic effects remains an unmet medical need.

As a novel non-hormonal approach to the management of endometriosis, dopamine receptor

agonists have been suggested to inhibit the angiogenesis process that is essential for the initiation, growth, invasion and recurrence of endometriotic lesions. Non-clinical and clinical data have suggested evidence of the primary pharmacological effects of dopamine receptor agonists in reduction of endometriotic lesions.

Quinagolide is a non-ergot-derived, potent and selective dopamine receptor 2 agonist and is approved in Europe as oral tablets under tradename NORPROLAC for the treatment of hyperprolactinaemia. In addition, it has been formulated into an extended-release vaginal ring for the treatment of endometriosis. The vaginal ring allows extended release of quinagolide for up to 35 days and can be replaced by a new vaginal ring in every menstrual cycle.

For further information on quinagolide vaginal ring, please refer to the Investigator's Brochure.[15]

1.2 Scientific Justification for Conducting the Trial

As an integral part of the endometriosis pathogenesis, the establishment of new blood supply is essential for survival and growth of endometriotic tissues when implanted outside the uterine cavity. This angiogenesis process is a critical mechanism that allows the development of endometriosis. The most prominently studied angiogenic factor is vascular endothelial growth factor (VEGF), which has been noted in endometriotic lesions and the peritoneal fluid of endometriosis patients.[16,17,18] A positive correlation between the severity of endometriosis and the level of VEGF concentration in peritoneal fluid has been observed.[18]

Dopamine 2 receptors are present in ectopic endometrium.[19] Dopamine agonist-mediated dopamine receptor 2 activation promotes VEGF receptor 2 endocytosis, preventing binding of VEGF to VEGF receptor 2. Administration of dopamine receptor 2 agonists was shown to reduce vascular permeability without affecting corpus luteum angiogenesis and function by partially inhibiting VEGF receptor 2 phosphorylation.[20] In addition, it has been shown that dopamine receptor 2 agonists diminish nerve fibre density in experimental endometriotic lesions.[21]

Non-clinical and clinical data have suggested evidence of primary pharmacological effects of quinagolide in reduction of endometriotic lesions. In mice with induced endometriosis, a significant reduction in the size of active lesions, cellular proliferation index and angiogenic gene expression was observed with high oral doses of quinagolide (50 or 200 µg/kg per day during a 14-day period) versus vehicle.[22] In a clinical trial involving 9 hyperprolactinaemic patients with endometriosis, it was observed at second-look laparoscopy that oral administration of quinagolide 25 µg to 75 µg once daily for 18-20 weeks induced a significant reduction in the overall size of endometriotic lesions, together with histological evidence of tissue degeneration and down-regulation of VEGF and proangiogenic cytokines.[23] Another clinical study in endometrioma patients demonstrated that cabergoline, a dopamine receptor 2 agonist, was significantly more effective in decreasing the size of endometrioma assessed by transvaginal ultrasound (TVU), compared to GnRH agonist triptorelin acetate after 3 months' treatment.[24]

As part of the clinical development programme of quinagolide for endometriosis, three phase 1 trials have been conducted with intravaginal administration of quinagolide in healthy volunteers in Germany and in United Kingdom. Based on the results of phase 1 trials, quinagolide administered as a vaginal ring avoids daily fluctuations of quinagolide levels as seen with oral administration and thereby has improved its tolerability. In addition, an extended-release formulation with replacement of the vaginal ring every menstrual cycle is more suitable for the long-term management of endometriosis than a daily formulation. Key results of each phase 1 trial are summarised below.

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

To provide supportive data on the mechanism of action of quinagolide, the present trial intends to evaluate the effect of quinagolide vaginal ring on the reduction of endometriotic lesions assessed by MRI. Since adenomyotic lesions are similar to endometriotic lesions and can be clearly identified by MRI, the effect of quinagolide vaginal ring on the reduction of adenomyotic lesions will also be evaluated in this trial.

MRI is considered the best imaging technique for mapping endometriosis.[25] Compared with ultrasound, MRI is less observer-dependent and more reproducible. A few studies have also shown that MRI is more accurate than TVU when correlating with histopathological findings of endometriosis / adenomyosis.[26,27] However, due to its high costs, MRI is often used in more complicated cases and is considered as a second-line imaging technique after ultrasound.[25] In the present trial, MRI is used as the primary imaging tool to assess endometrioma, DIE, and adenomyosis and TVU is used to assess endometrioma.

Of the three sub-types of endometriosis, endometrioma and DIE can be visualised by MRI with a fairly high sensitivity (82%-90% for endometrioma and 67%-83% for DIE) and specificity (91%-98% for endometrioma and >89% for DIE).[10,28] Due to its high concentration of blood and proteins, endometrioma demonstrates high signal intensity on T1-weighted images and low signal intensity on T2-weighted images.[29] Deep infiltrating endometriosis can involve the pelvic ligaments, anterior rectosigmoid colon, bladder, uterus, and cul-de-sac, as well as surgical scars; the lesions often have

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

poorly defined margins and T2 signal hypointensity as a result of fibrosis.[29] The presence of sub-centimetre foci with T2 hyperintensity representing ectopic endometrial glands within these infiltrating fibrotic masses may help establish the diagnosis.[29]

The accuracy of MRI in the diagnosis of adenomyosis has long been established with a sensitivity of 88%-93% and a specificity of 67%-91%.[11] On T2-weighted images, adenomyosis appears as a poorly-marginated low-signal-intensity area and additional small high-signal-intensity areas referring to ectopic endometrium.[27] These MRI findings are related to the thickening or hyperplasia of the junctional zone and a maximum junction zone thickness of ≥12 mm has been widely used as the major criterion for the diagnosis of adenomyosis.[8,27,30]

With its high spatial resolution, MRI can also provide additional information on tissue structure and functionality. The use of dynamic, contrast-enhanced (DCE) perfusion imaging biomarkers can highlight endometriotic tissues with high angiogenesis expression and thereby evaluate the anti-angiogenic effect of quinagolide through the assessment of tissue vascularisation and vessel permeability before and after the treatment.[10] Diffusion imaging biomarkers can capture changes in water molecules behaviour within tissue microarchitectures, allowing to quantify the diffusion coefficient associated with cell density and interstitial space disruption, both of which may help define the nature of lesions, especially for endometrioma and adenomyosis.[10]

In summary, as a novel non-hormonal drug inhibiting angiogenesis, quinagolide has the potential to address the unmet medical need for long-term treatment of endometriosis and/or adenomyosis. The present phase 2 trial aims at assessing the effect of quinagolide vaginal ring on the reduction of lesions in women with endometrioma, DIE and adenomyosis. The results of the present trial will provide further evidence on the mechanism of action of quinagolide, help identify subgroups of endometriosis patients that might benefit from quinagolide, and support the sponsor's decisions on further development of the clinical programme on quinagolide.

1.3 Benefit / Risk Aspects

Benefits

In each subgroup, subjects will be randomised in a 2:1 ratio to quinagolide vaginal ring or placebo vaginal ring and may benefit from relief of their symptoms if the treatment is effective. Subjects participating in this trial may also benefit from a comprehensive survey of their diseases by the MRI examination, which is not routinely performed in standard clinical practices. Subjects will also be reimbursed for travel expenses and for the analgesic use for the management of endometriosis or adenomyosis pain in line with local reimbursement policies and regulations. It should be noted that the treatment and trial-related procedures are provided to the participating subjects free of charge, as Ferring compensates the investigational sites for their expenses. If a 3-month wash-out is required for participation in the trial, subjects can be compensated for resuming their original treatment after the end-of-trial in line with local reimbursement policies and regulations.

Risks

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

Risks – Investigational Medicinal Product

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

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

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

Quinagolide is approved as an oral tablet formulation under tradename NORPROLAC for the treatment of hyperprolactinaemia in Europe and in some other countries. The estimated cumulative exposure of quinagolide until now is more than 280,000 patient years, when administered as an oral tablet in the approved dose range of 25-300 µg or higher. The general safety profile of quinagolide is characterised by adverse events involving the gastrointestinal tract and central nervous system. The most frequent adverse events (all reported as very common, i.e. at a frequency of ≥10%) in

relation to oral administration of quinagolide tablets are nausea, vomiting, headache, dizziness and fatigue. They occur predominantly during the first few days of the initial treatment or, as a mostly transient event, following dosage increase.

A serious but very rare risk associated with quinagolide oral tablets is syncope (<0.01%), which can be secondary to orthostatic hypotension. Orthostatic hypotension occurs at a frequency of 1-10% among patients treated with quinagolide oral tablets. As a risk mitigation, subjects should be instructed to lie down when experiencing dizziness or light-headedness during the initiation of the treatment. Dopamine agonists other than quinagolide have been associated with sudden sleep onset episodes, particularly in patients with Parkinson's disease, and this has resulted in a general warning for the entire class of drugs. In rare cases (i.e. at a frequency of 0.01% to 0.1%), treatment with dopamine agonists has been associated with the occurrence of acute psychosis, which is reversible upon discontinuation.[31] Impulse control disorders involving pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating were rarely reported in association with the use of dopamine receptor agonists including quinagolide for the treatment of Parkinson's disease.[32] Ergot-derived dopamine agonists have been associated with an increased risk of fibrosis of the heart valves possibly through activation of 5-hydroxytryptamin 2B receptor (5-HT2B). Quinagolide is a non-ergot-derived dopamine agonist and is not known to have any 5-HT-receptor activity at clinically relevant doses.[33,34] Furthermore, no cases of valvular heart disease have been reported with quinagolide.

Quinagolide is not an embryotoxic or teratogenic agent. No adverse effects on embryos or fetuses were observed in the reproductive toxicity studies in rats and rabbits.[15] Based on available clinical data, exposure to quinagolide during early pregnancy has not been shown to increase the risk of pregnancy losses or congenital malformations compared with a normal pregnant population. Single-barrier contraception is considered to be adequate in the present trial. Condoms and contraception counselling will be offered throughout the trial and condoms will be provided to all subjects at almost every visit to avoid occurrence of pregnancy during participation of the trial. As a precautionary measure, a urine pregnancy test will be performed once per menstrual cycle in the present trial. If the test result is positive and confirmed by a serum βhCG test, the subject will be discontinued from the trial immediately and will be followed up until delivery.

Procedures in this trial are mainly MRI, TVU and blood sampling, which are non-invasive or minimally invasive. The MRI is a painless radiology technique that has the advantage of avoiding the harmful effects of ionizing radiation. Due to the use of the strong magnet, MRI is contraindicated in patients with internal or external metallic objects such as implanted devices or leg braces. Adverse events associated with MRI are very rare (<0.01%).[35] The majority of those adverse events are body temperature increase from the radio-frequency energy and hearing problems due to the noises of the gradient magnetic fields.[35] The use of contrast media in MRI may carry a risk of allergic reaction to the contrast media, with an incidence of acute adverse reactions varying from 0.17% to 2.4%.[36] Fasting may cause dizziness, headache, stomach discomfort or fainting, but fasting is required for only 3-4 hours before the MRI examination. The TVU

examinations may be associated with mild discomfort and a very rare risk of infection. The blood sampling might be associated with mild discomfort, bruising and a very rare risk of infection.

For further information on quinagolide vaginal ring, please refer to the Investigator's Brochure.[15]

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

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)

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

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

Primary Endpoint

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

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

Exploratory Endpoints

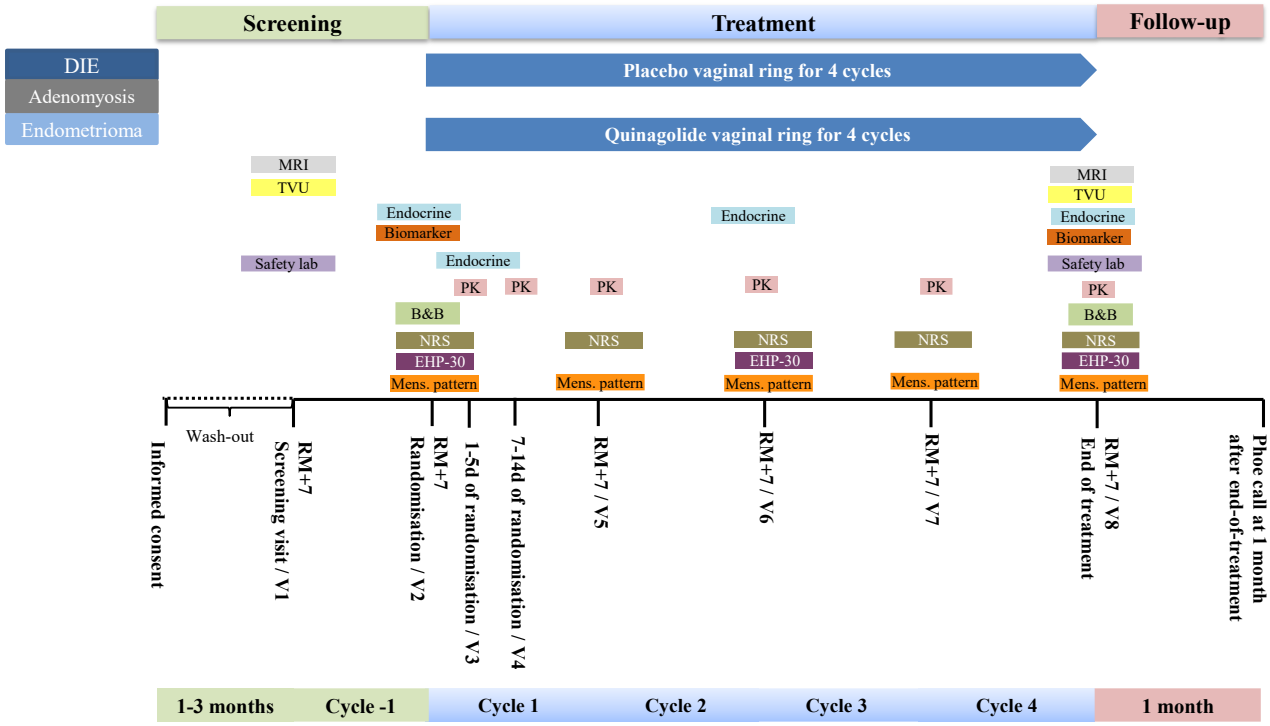
- Changes in the MRI-derived perfusion imaging biomarkers of AUC, K^{trans}, k_{ep}, v_e, v_p at cycle 4
- Changes in the MRI-derived diffusion imaging biomarkers of ADC, D, D* and f at cycle 4
- Changes in the sizes of uterine fibroids on MR images at cycle 4
- Changes in the sizes of uterine fibroids assessed by TVU at cycle 4
- Changes in circulating levels of 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 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

3.1.1 Trial Design Diagram

A diagram illustrating the trial design is shown in Figure 3-1.



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 Overall Design and Control Methods

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.

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 (approximately 4 months) and including a wash-out period (only applicable to subjects using some hormonal products) 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 return of menses, 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 a 2:1 ratio to receive quinagolide vaginal ring or placebo vaginal ring for four menstrual cycles (cycles 1, 2, 3 and 4). 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.

Transvaginal ultrasound 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 randomisation 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.

A follow-up 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.

3.1.3 Trial Schedule

First patient first visit (FPFV)	Q3 2019
Last patient last visit (LPLV)	Q2 2021

3.2 Planned Number of Trial Sites and Subjects

It is planned to randomise approximately 72 subjects, with approximately 24 subjects in each sub-group, from 8-12 sites in Europe. It is estimated that 100 subjects will be screened in this trial.

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

3.3 Interim Analysis

No interim analysis is planned for this trial.

3.4 Data Monitoring Committee

No Data Monitoring Committee is planned for this trial. During the trial, the internal Safety Management Team at Ferring will evaluate blinded safety data at least quarterly.

3.5 Discussion of Overall Trial Design and Choice of Control Groups

3.5.1 Trial Design

The primary objective of the trial is to evaluate the effect of quinagolide administered as an extended-release vaginal ring compared to placebo vaginal ring on reduction of lesions in women with endometrioma, DIE and/or adenomyosis.

This is a randomised, double-blind, placebo-controlled trial. The double-blind, placebo-controlled clinical trial has a long history as the standard for investigations of new drugs and is commonly used in clinical trials of endometriosis (e.g. ClinicalTrials.gov NCT00225199, NCT01931670). Currently, there is no approved non-hormonal treatment of endometriosis. Moreover, the placebo response has not been rigorously characterised with respect to endometriotic/adenomyotic lesion reduction. A placebo group is justified for this trial in order to properly evaluate the absolute treatment effect of quinagolide on lesion reduction. Furthermore, there is a need to account for the placebo effect beyond lesion sizes, such as pain reduction and vessel permeability, for a proper and comprehensive evaluation of the anti-angiogenic treatment effect of quinagolide. In this trial, ethical concerns of using placebo controls have been addressed by allowing subjects to use analgesics for pain relief as needed. In addition, the use of analgesics can help prevent dropouts due to lack of efficacy. With a randomisation ratio of 2:1, the chance for a subject being randomised to the placebo group is decreased, compared to a randomisation ratio of 1:1.

A double-blind design will ensure blinding and thereby unbiased evaluations of the primary endpoint and the secondary endpoints related to MRI findings assessed by the central imaging laboratory. Similarly, the blinding of investigators and subjects can guarantee unbiased evaluations of the secondary endpoints related to the PROs. Precautions and measures taken to ensure double-blinding of the trial are described in detail in section 3.5.3.

In this trial, there are three sub-groups of subjects, with each sub-group representing one sub-type of lesions, i.e. endometrioma, DIE and adenomyosis. Epidemiology studies have shown that endometriosis and adenomyosis can often coexist in the same subject.[37,38] Since MRI can assess all pelvic compartments comprehensively at one time, it is feasible and convenient to examine any of the three sub-types of lesions presented in the subject in one MRI examination. The design of three separate sub-groups, with subjects on placebo in each sub-group, can ensure changes in each sub-

type of lesions are assessed against placebo and thereby help identify the sub-type of lesions that responds best to the treatment.

Although a multi-centre setting can help guarantee that the required number of subjects can be recruited within a reasonable time and also support the subsequent generalisation of the results, this trial is limited to a few trial centres with machines of high field strength (3T) and of limited brands to minimise variability of results. In addition, the standardisation of the MRI preparations, sequences and procedures in the trial-specific MRI manual, cross calibration among sites as well as the central reading and analyses of images by the same specialised laboratory have to a great extent been incorporated in the design of this trial to minimise variations across sites.

The treatment period of the trial lasts for four menstrual cycles, which approximately corresponds to the active treatment duration of 18-20 weeks in the second-look laparoscopy study, where significant reductions in endometriotic lesions were observed following oral administration of quinagolide up to 75 µg.

A non-hormonal single-barrier contraception method (i.e. condom) is required for subjects participating in the present trial. Condom is the only feasible contraception method in this trial, as other contraception methods such as oral contraceptives and intrauterine devices (IUDs) can potentially interfere with the assessment of lesions. Throughout the trial, contraception counselling and condoms will be offered to avoid occurrence of pregnancy during treatment. As a precautionary measure, a urine pregnancy test will be performed once per menstrual cycle in the present trial. If the test result is positive and is confirmed by a serum βhCG test, the subject will be discontinued from the trial immediately.

3.5.2 Selection of Endpoints

The primary endpoint of the present trial is the change in the size of endometrioma, DIE and adenomyosis lesions summed by type on MR images compared to placebo at cycle 4.

It is considered clinically sufficient to evaluate changes in the endometriotic / adenomyotic lesion sizes after four menstrual cycles, because MRI may not be able to detect minimal changes within a short period and endometriotic / adenomyotic lesions are much less aggressive than solid tumours, the latter of which are usually evaluated only every 3 months per standard clinical practices. In a similar trial assessing adenomyotic lesions by MRI, lesion sizes were evaluated after 6 months of treatment with levonorgestrel-releasing IUDs, indicating a mean (±SE) maximal junction zone thickness of 17.7 (±0.9) mm at baseline and of 13.1 (±0.8) mm at 6 months ($p<0.001$).[39]

The primary endpoint and primary analysis focus on lesions of ≥10 mm at baseline, which are considered “measurable” lesions that are subject to “reproducible repeated measurements” at both baseline and at cycle 4. This approach is similar to the selection of target lesions in solid tumours and follows the revised Response Evaluation Criteria in Solid Tumours (RECIST) guideline (version 1.1).[40]

A relatively strict timing of the MRI assessment, i.e. on a day without bleeding, is required in the trial to avoid biases and errors due to the mucosal and myometrial physiological changes during bleeding. This practice is in line with the recommendations of radiologists.[3,41]

To address measurement limitations of MRI, lesions with a clinically relevant size reduction of ≥5 mm at cycle 4 are further investigated as part of secondary endpoints. Number of new lesions and disappearing lesions (defined in section 7.1) are evaluated to capture lesion progression and regression, even if their sizes may not necessarily be measurable. In addition to lesion size, volume of endometrioma and DIE lesions are also measured as a complementary metric of lesions by MRI. Since TVU is commonly used in clinical practices and can also measure endometrioma, the sizes of endometrioma will be evaluated by TVU as a secondary endpoint.

Other secondary endpoints include B&B, NRS and EHP-30, which are all widely used PROs on symptoms and quality of life of endometriosis patients. The B&B scale[42] has been widely used for endometriosis patients in other endometriosis trials and is selected in the present trial for historical comparison. Likewise, the validated 11-point NRS is commonly used in clinical trials to quantify pain intensity and is administered on a monthly basis in this trial. Since endometriosis patients can also have a compromised quality of life, the EHP-30 questionnaire[43] will be administered to assess any changes in quality of life associated with treatment.

Plasma concentrations of quinagolide and its active metabolites (M1 and M2) will be assessed to allow estimation of population pharmacokinetic (PK) parameters and investigation of the exposure-response relationship with lesion reduction being the response in the present trial. Endocrine parameters related to the effect of quinagolide will be evaluated. Safety endpoints cover the monitoring of adverse events and routine safety laboratory parameters.

Exploratory endpoints include perfusion imaging biomarkers to assess the angiogenesis expression of tissues and diffusion imaging biomarkers to evaluate cell density, thereby providing evidence on the mechanism of action of quinagolide. Similarly, plasma and serum endometriosis biomarkers of VEGF, PlGF, IL-6, CA125 and sFlt-1 can help monitor the treatment response to quinagolide. The treatment effect on uterine fibroids will also be explored.

3.5.3 Blinding

The present trial is double-blind. Subjects, investigators, radiologists, other trial staff and MRI analysers at the central imaging laboratory will be blinded to treatment allocation during the conduct of the trial. Blinding is achieved by randomising subjects in a 2:1 ratio to a vaginal ring containing quinagolide dose load 1080 µg or placebo, both of which are identical in appearance, flexibility and softness.

Similarly, the Ferring clinical team (e.g. data manager, statistician, clinical trial manager, clinical project leader, medical writer, pharmacovigilance physician, pharmacovigilance manager and

medical officer) will be blinded to treatment allocation until breaking of the blind. The blind will be broken when the trial database is declared clean and is released to the responsible statistician.

Central laboratory analysis results of some endocrine parameters (prolactin, TSH and IGF-1) after randomisation and results of endometriosis biomarkers throughout the trial will not be available to site or sponsor staff until breaking of the blind. To avoid potential speculation of treatment allocation by comparing current pain scores against previous scores, subjects are not given access to historically reported data.

3.5.4 Selection of Dose in the Trial

Selection of quinagolide vaginal ring dose is based on safety, tolerability and pharmacokinetics data obtained from the completed phase 1 trials.

Oral administration of quinagolide at doses up to 75 µg once daily for 18-20 weeks appeared to reduce the size of lesions in endometriosis patients with hyperprolactinaemia.[23] The repeated oral administration and intravaginal administration of 75 µg quinagolide tablets once daily for 5 days in the first phase 1 trial (Trial 000076) showed that intravaginal administration of quinagolide tablets was associated with higher exposure of quinagolide and reduced levels of metabolites, demonstrating that intravaginal administration circumvents the first pass metabolism. However, it was well tolerated with lower incidences of treatment-related adverse events, compared with oral administration. In addition, intravaginal administration had a slow absorption with approximately 8 hours to reach the C_{max} of quinagolide, compared with oral administration (T_{max} about 1 hour).

In the subsequent trial (Trial 000155), following administration of the highest dose of quinagolide vaginal ring, the mean quinagolide C_{max} of 10.9 pg/mL does not exceed the mean C_{max} of 13 pg/mL observed with the 75 µg intravaginal tablet. Following the initial peak, the concentrations are similar to the mean C_{max} of 8 pg/mL observed with the 75 µg oral tablet. In addition, quinagolide administered as a vaginal ring avoids daily fluctuations of quinagolide levels as seen with oral administration.

Based on the above data, the highest dose load of quinagolide vaginal ring at a target release rate of 13.5 µg/day seems to have the most favourable pharmacokinetic profile associated with reduction in the size of endometriotic lesions while being well-tolerated and is therefore selected for this trial.

3.5.5 Selection and Timing of Dose for Each Subject

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

Subjects will be instructed to insert the assigned ring in the upper part of the vagina at RM+7 visits, a timing that corresponds to the stop or the end of menstrual bleeding and is convenient for administration of a vaginal product, which can therefore easily be remembered and followed by subjects. The vaginal ring will be kept in the vagina continuously for one menstrual cycle until being replaced by the next ring on RM+7 of the next cycle when the subject visits the clinic. Thus, quinagolide will be given sufficient time to inhibit the endometriotic / adenomyotic lesions prior to return of the menses in the next cycle, when most of the severe pain occurs.

3.5.6 Selection of the Trial Population

The trial population consists of subjects presenting endometrioma, DIE and/or adenomyosis confirmed by the MRI examination. As mentioned in section 1.2, these are the three sub-types of lesions that can be visualised by MRI with a fairly high sensitivity and specificity and therefore the selected trial population is considered suitable for using MRI to evaluate lesion changes. As supplementary information, prior surgeries of eligible subjects will be recorded in medical history.

To be eligible for this trial, subjects should have at least one of the following sizes of lesions identified by MRI: endometrioma (≥20 mm), DIE (≥15 mm), and/or adenomyosis (junctional zone thickness ≥12 mm or focal lesion ≥15 mm). The selected thresholds of lesions sizes ensures that eligible subjects present relatively large lesions, whose sizes and whose changes in sizes can be well captured by MRI, although every lesion ≥10 mm will be measured at baseline.

The trial will include pre-menopausal women aged between 18 and 45 years and thereby cover the age span of the most endometriosis and adenomyosis patients. Eligible women are required to have menstrual cycles of 24 to 35 days, covering the release duration of quinagolide vaginal ring.

The exclusion criteria incorporate the contraindications to NORPROLAC and to MRI examination.

3.5.7 Follow-up Procedures

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

Access to Therapy after End-of-Trial

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

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

4.1.1 Inclusion Criteria

1. Informed consent signed and dated prior to any trial-related procedures.
2. In good physical and mental health to participate in the trial.
3. Pre-menopausal females between the ages of 18-45 years (both inclusive) at the time of signing the informed consent.
4. A menstrual cycle of 24-35 days (both inclusive) based on observation made in the absence of drugs that can affect the cycle length (e.g. oral contraceptives) prior to the screening visit.
5. Body mass index (BMI) of 18-35 kg/m^2 (both inclusive) at screening.
6. Confirmation of deep infiltrating endometriosis (DIE) (lesion size ≥15 mm), endometrioma (≥20 mm) or adenomyosis (maximum junctional zone thickness ≥12 mm or focal lesion ≥15 mm) by high-resolution MRI at screening.
7. Transvaginal ultrasound documenting a uterus with no abnormalities of endometrium and presence of at least one ovary with no clinically significant abnormalities at screening. Note that presence of uterine fibroids are not exclusionary but presence of any submucosal fibroids or polyps are exclusionary.
8. Willing and able to use a non-hormonal single-barrier method (i.e. condom) for contraception from the start of screening to the end-of-treatment. This is not required if adequate contraception is achieved by vasectomy of the male sexual partner, surgical sterilisation (e.g. tubal ligation and blockage methods such as ESSURE) of the subject, or true abstinence of the subject (sporadic sexual intercourse with men requiring condom use).
9. Willing to avoid the use of vaginal douches or any other intravaginally administered medications or devices (except for tampons) from randomisation to the end of treatment.
10. Documentation of normal cervical cytology, or negative human papilloma virus (HPV) results for high-risk viral subtypes upon presence of atypical squamous cells of undetermined significance, based on test(s) performed within 24 months of randomisation.
11. Willing and able to comply with trial procedures, including attending scheduled visits and adherence to treatment plan.

4.1.2 Exclusion Criteria

1. Use of depot medroxyprogesterone acetate (MPA) within 10 months prior to the screening visit.
2. Use of gonadotropin-releasing (GnRH) agonists (3-month depot) or dopamine agonists within 6 months prior to the screening visit.
3. Use of GnRH agonists (1-month depot or nasal spray), GnRH antagonists, aromatase inhibitors, danazol, birth control implants (e.g. NEXPLANON), progestogen or levonorgestrel-releasing IUD within 3 months prior to the screening visit.

4. Use of hormonal contraceptives (including combined oral contraceptive pill, transdermal patch, and contraceptive ring) and copper IUDs within 1 menstrual cycle prior to the screening visit.
5. Undiagnosed abnormal vaginal bleeding within the last 3 months of the screening visit.
6. History of recurrent bacterial, fungal or viral vaginal infection (i.e. ≥4 episodes within a year).
7. History of malignancy within 5 years prior to the screening visit, except for adequately managed basal cell carcinoma and squamous cell carcinoma of the skin.
8. History of orthostatic hypotension or recurrent syncope.
9. History of mental illness including occurrence of acute psychosis, bipolar disorder and schizophrenia (except for well-controlled mild or moderate anxiety and/or depression with no changes to interventions for 3 months prior to the screening visit).
10. History of sudden sleep onset episodes.
11. Known diagnosis of impulse control disorders including pathological gambling, compulsive buying, hypersexuality, and binge eating.
12. Known positive results of Human Immunodeficiency Virus (HIV) antibody tests.
13. Any other incidental, clinically significant abnormal findings than endometriotic / adenomyotic lesions identified at the screening MRI assessment (e.g. suspected tumour).
14. Any clinically significant abnormal findings from vital signs, blood tests of haematology and clinical chemistry at screening, including alanine aminotransferase (ALT) >2.5 times upper limit of normal (ULN) or bilirubin >1.5 times ULN or creatinine >1.5 times ULN.
15. Any clinically significant abnormal findings at physical examination at screening.
16. Any vaginal or vulvar lesions that would interfere with vaginal ring usage.
17. Current pregnancy as confirmed by a positive serum pregnancy test at screening or planning a pregnancy within the duration of the trial, or currently breast-feeding or less than 6 months post-partum prior to the screening visit.
18. Planned surgical treatment of endometriosis or adenomyosis during the duration of the trial.
19. Continuous use of strong opioids (e.g. morphine) and/or illicit drugs (e.g. marijuana and amphetamine) for more than 2 weeks within 6 months prior to the screening visit.
20. Alcohol abuse (>14 units of alcohol a week) within 2 years prior to the screening visit.
21. Previous or current participation in a clinical trial involving a non-registered investigational medicinal product within 1 month of screening. If the trial involves a hormonal drug, the exclusion criteria 1-4 shall apply.
22. Contraindications to MRI such as having internal/external metallic devices and/or accessories (e.g. cardiac pacemakers and leg braces).
23. Hypersensitivity to any active ingredients, excipients or other components of medicinal products used in the trial, including quinagolide vaginal ring, placebo vaginal ring and any products used for MRI examination.

4.2 Method of Assigning Subjects to Treatment Groups

4.2.1 Recruitment

The participating subjects will be recruited from sites included in the trial. Advertisements may be used if approved by relevant Independent Ethic Committees (IECs) in line with local regulations.

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

4.2.2 Randomisation

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

An independent statistician will create a computer-generated randomisation list and randomisation is performed centrally through the Interactive Response Technology (IRT) system prior to the insertion of the first vaginal ring. Thereby each subject will receive a unique randomisation number generated in the IRT system. Randomisation is stratified by site.

4.3 Restrictions

4.3.1 Prohibited Medications / Therapies

Prohibited Medications / Therapies before the Trial and during the Trial

The following concomitant medications and therapies are prohibited from the following period indicated before the screening visit until the end-of-treatment:

Prohibited medications / therapies	Examples	Minimum prohibited period before the screening visit
Depot MPA	DEPO-PROVERA	10 months
GnRH agonist (3-month depot injection)	LUPRON, ZOLADEX	6 months
Dopamine agonist	bromocriptine cabergoline (DOSTINEX)	6 months
GnRH agonist (1-month depot injection or nasal spray)	LUPRON, ZOLADEX, SYNAREL	3 months
Progestogen and levonorgestrel-releasing IUD	MIRENA	3 months
GnRH antagonist		3 months
Aromatase inhibitor		3 months
Danazol	CYCLOMEN	3 months
Birth control implants	NEXPLANON	3 months
Hormonal contraceptives* and copper IUDs	combined oral contraceptive pill, transdermal patch and contraceptive ring (NuvaRing)	1 menstrual cycle
Prohibited medications / therapies from randomisation to the end-of treatment		
Vaginal douches or any other intravaginally administered medications or devices		

*Discontinuation of hormonal contraceptives should follow the labelling of the product (e.g. completing the current cycle of contraceptives before wash-out). Emergency contraceptives are allowed from randomisation to the end-of-trial.

Prohibited Therapy after the Trial

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

4.3.2 Other Restrictions

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

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

4.4 Withdrawal Criteria

Withdrawal from Trial

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

The investigator has the right to withdraw a subject from the trial if:

- The subject requires a medical or surgical treatment that is prohibited by the protocol

- The subject becomes pregnant as confirmed by urine and serum βhCG pregnancy tests
- The subject becomes menopausal as confirmed by blood tests for endocrine parameters
- There are other medical or safety reasons at the discretion of the investigator

Since it is important to collect efficacy and safety data of all randomised subjects, unnecessary withdrawal of subjects should be avoided.

Every effort should be made to invite withdrawn subjects to complete the end-of-trial assessments including the end-of-trial MRI as applicable. For any discontinuation, the investigator will obtain all the required details and document the date of the premature termination and the main reason in the e-CRF.

Withdrawal of Consent

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

4.5 Subject Replacement

A subject can only be assigned one screening number and one randomisation number. The screening and randomisation number are unique and cannot be re-used. Subjects who discontinue prematurely from the trial after randomisation are not to be replaced.

5 TREATMENTS

5.1 Treatments Administered

5.1.1 Investigational Medicinal Products

The investigational medicinal products (IMPs) in the present trial will be supplied as vaginal rings containing quinagolide 1080 µg or its matching placebo. Quinagolide vaginal ring is a vaginal delivery system which allows for the extended release of quinagolide for up to 35 days. The strength of quinagolide vaginal ring investigated in the present trial has a target release rate of quinagolide 13.5 µg/day. Quinagolide or placebo vaginal ring is inserted at the RM+7 visit at the site and is kept in the vagina continuously until being replaced by a new ring at the RM+7 visit of the next cycle.

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

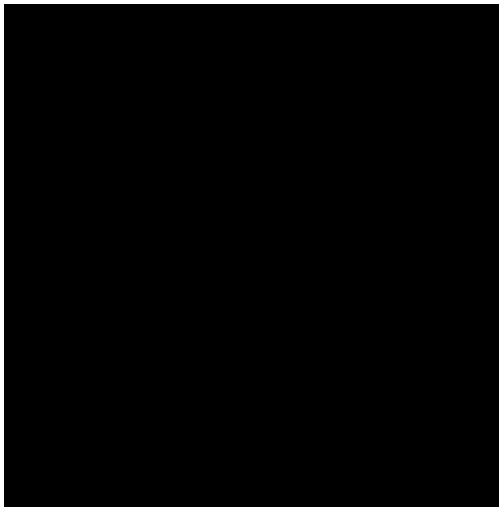
The vaginal ring will be inserted and removed by the subject herself at the RM+7 visits to clinic by following the standard instruction for use, irrespective of whether the subject is still experiencing menstrual bleeding. If needed, supervision by site staff can be provided and lubricants allowed for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

5.1.2 Non-Investigational Medicinal Product

No non-investigational medicinal product will be provided in this trial.

5.2 Characteristics and Source of Supply

All IMPs are provided by Ferring and will be handled according to the principles of Good Manufacturing Practice (GMP). All sites will be provided with quinagolide and placebo vaginal rings in amounts sufficient for the trial. Quinagolide vaginal ring and placebo vaginal ring are indistinguishable with identical appearance. All vaginal rings are soft, flexible, off-white, translucent, toroid shaped rings with a major diameter of 54 mm and a minor diameter of 4.1 mm. An illustration of the vaginal ring is provided in Figure 5-1.



The content of the quinagolide and placebo vaginal ring is provided in Table 5-1.

5.3 Packaging and Labelling

Packaging and labelling of the IMPs will be performed under the responsibility of the Clinical Trial Supply Department at Ferring Pharmaceuticals A/S in accordance with GMP, Annex 13, EudraLex Volume 4 and national regulatory requirements.

Quinagolide vaginal ring and placebo vaginal ring will be packaged in an individual foil moisture barrier pouch with re-closable gripper and tear notches in identical appearances. The IMPs will be labelled with trial-specific labels in accordance with applicable requirements.

5.4 Conditions for Storage and Use

The site staff will ensure that the medicinal products will be stored in appropriate conditions in a secure location with controlled access. The storage compartment shall be monitored regularly and

the temperature shall be documented in accordance with the instructions provided by the sponsor.

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

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

For information on warnings, precautions and treatment of overdose, please refer to the Investigator's Brochure for the IMP.[15]

5.5 Blinding / Unblinding

5.5.1 Blinding

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

All packaged IMP kits will be indistinguishable with identical appearance and will be labelled with random identification numbers which are linked to the treatment allocation. Once the subject is assigned a unique randomisation number in the IRT system, site staff can access the IRT system to obtain an identification number for the vaginal ring to dispense to the subject, with both the site staff and the subject blinded to the treatment allocation. In case of ring replacement, the identification number for the replacement ring will also be obtained from the IRT system. All vaginal rings will be indistinguishable with identical appearance, flexibility and softness. Subjects, investigators, radiologists, other trial staff as well as in-field monitors and MRI analysers at the central imaging laboratory will be blinded to treatment allocation throughout the trial.

The personnel at the central laboratory analysing blood samples for quinagolide and its metabolite concentration will be unblinded to treatment allocation but the personnel at the other central laboratory analysing other blood samples will be blinded to treatment allocation throughout the trial. Ferring clinical team, e.g. data manager, statistician, trial manager, clinical project leader, medical writer, pharmacovigilance physician, pharmacovigilance manager and medical officer will be blinded to treatment allocation until breaking of the blind. The blind will be broken when the trial database is declared clean and is released to the responsible statistician.

The randomisation list will not be available to any person involved in the conduct and evaluation of the trial until the trial database is declared clean and locked. Likewise, the treatment allocation information will not be accessible to investigators, trial staff at the site or central laboratory personnel during the trial.

5.5.2 Unblinding of Individual Subject Treatment

An emergency unblinding procedure will be available to the investigator and designated persons at Ferring through the IRT system. It is the investigator's responsibility to decide whether it is medically necessary to know the investigational product the subject receives (i.e. unblinding) to ensure the subject's welfare and safety, and thereby the responsibility to break the blind for individual subjects in emergency situations resides with the investigator.

Breaking of the blind for individual subjects in emergency situations could be required in case of a suspected unexpected serious adverse reaction (SUSAR) or in case of an important adverse event where the knowledge of the IMP in question is required for therapeutic decisions for the management of the subject. If possible, the investigator should inform the sponsor before unblinding. If this is not possible and the event requires immediate unblinding by the investigator, the investigator must inform the sponsor of the unblinding as soon as possible afterwards and provided the rationale for unblinding.

The investigator/person who unblinds a subject's treatment will use the unblinding module of the IRT system, in which he/she is required to enter a password before the treatment code can be broken. The IRT automatically records when and by whom the code is broken. The investigator must record the event of unblinding in the subject's medical record, including the reason for unblinding, but not the treatment allocation if this can be avoided.

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

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

Information on whether the blind has been broken for any subjects will be transferred to the e-CRF. In case of emergency or accidental unblinding, information on when and by whom the code is broken will be transferred to the e-CRF and the reason for unblinding will also be recorded in the e-CRF. All information about emergency or accidental unblinding must be collected before the database is declared clean and is released to the responsible statistician.

In case the IRT cannot be accessed and hence the emergency unblinding cannot be performed within the IRT system, the investigator should contact Ferring Global Pharmacovigilance using the

contact details given below:

Global Pharmacovigilance, Ferring Pharmaceuticals A/S

[redacted]

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

5.6 Treatment Compliance

5.6.1 Dispensing and Accountability

The IMP must only be dispensed to and inserted by subjects who meet the eligibility criteria and are randomised in the trial. The site staff will use the IRT system to assign and dispense IMPs. The investigator (or his/her delegated personnel) will also record the dates and quantities of IMPs dispensed to and returned by each subject, as well as manage the overall drug accountability for each subject within the IRT system. The in-field monitor will review and verify the drug accountability of the IMPs throughout the trial. Any discrepancies will be documented.

5.6.2 Assessment of Compliance

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

5.7 Return and Destruction of Medicinal Products

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

All unused medicinal products will be accounted for and must be destructed in a certified way.

5.8 Auxiliary Supplies

Sites will be provided with lubricants for ring insertion and/or removal. Any unused supply of lubricants will be returned or destructed upon trial site closure.

6 TRIAL PROCEDURES

6.1 Trial Flow Chart

Table 6-1 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 moths 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	
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 products (e.g. combined oral contraceptive pill, progestogen and levonorgestrel-releasing IUD) 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.

6.2 Screening

Potential participants will be scheduled to come to the clinic for the screening assessments. The screening period should not exceed 5 months. 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).

6.2.1 Wash-out (As Applicable)

Subjects who are currently using some hormonal products (e.g. combined oral contraceptive pill, progestogen and levonorgestrel-releasing 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). The wash-out period will be approximately 1 to 3 months, depending on the applicable requirements for different hormonal products (see section 4.3.1).

The following must take place if a wash-out period is required, prior to initiating the wash-out:

- Signed and dated written informed consent, obtained prior to any trial-related procedures
- Check of inclusion and exclusion criteria (those which are possible to check at this stage)
- Recording of use of concomitant medications (any hormonal treatment of endometriosis / adenomyosis within the last 6 months prior to the signed informed consent for participation in the trial and any other concomitant medications within the last 3 months prior to the signed informed consent for participation in the trial)
- Recording of adverse events (from the date of signed informed consent)
- Reminding the subject to contact trial staff as soon as having return of menses and to attend the RM+7 visit (visit 1)

6.2.2 Screening Visit / Visit 1 (Start of Cycle -1)

Subjects will attend the screening visit (visit 1), scheduled on 6-10 days after return of menses (RM+6-10). This is also the start of the screening cycle (cycle -1).

The following must take place for those subjects who do NOT require a wash-out period:

- Signed and dated written informed consent, obtained prior to any trial-related procedures

The following procedures must be performed for all subjects:

- Check of inclusion and exclusion criteria (those which are possible to check at this stage)
- Demographics (age, ethnicity, race)
- Collection of the following data:
  - Medical history
  - Menstrual history
  - Reproductive history
- Body measurement (body weight, height) [*note*: these are used for calculation of BMI]

- Vital signs
- Physical examination
- Gynaecological examination
- Cervical cytology test [*note*: performed only for subjects who do not have a cervical cytology test result within 24 months of the screening visit]
- Transvaginal ultrasound (record the sizes of endometrioma / uterine fibroids, if any)
- Urine pregnancy test [*note*: results must be negative]
- Blood collection for central laboratory analysis of:
  - Safety laboratory tests of clinical chemistry and haematology parameters

  [*note*: the results of both tests must be available prior to randomisation]
- Recording of use of concomitant medications (any hormonal treatment of endometriosis / adenomyosis within the last 6 months prior to the signed informed consent for participation in the trial and any other concomitant medications within the last 3 months prior to the signed informed consent for participation in the trial; or from last visit)
- Recording of adverse events (from the date of signed informed consent; or from last visit)
- Dispensing of condoms and reminding the subject to use proper contraception
- Reminding the subject of the MRI examination and the RM+7 visit at the end of cycle -1

The following procedures will be performed at the site's affiliated radiology department, if subjects are considered eligible for the trial based on the inclusion and exclusion criteria assessed at this time point:

- MRI examination [*note*: performed at or close to this visit when the subject has no bleeding. Fasting (no food or drink) for 3-4 hours in advance]

6.2.3 Randomisation / Visit 2 (RM+7 of Cycle -1)

Subjects will attend visit 2, scheduled on RM+6-10 of cycle -1 (i.e. the end of cycle -1).

The following must take place prior to randomisation:

- Urine pregnancy test [*note*: results must be negative]
- Vital signs
- Check those inclusion and exclusion criteria that were not possible during screening

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

- Randomisation, i.e. assignment to a unique randomisation number in the IRT system and thereby allocated to placebo vaginal ring or quinagolide vaginal ring dose load 1080 µg

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

- Ensuring the completion and legibility of NRS by the subject
- Ensuring the completion and legibility of the EHP-30 questionnaire by the subject
- Completing the first part of B&B scale based on the subject's verbal responses

- Investigator completing the second part of B&B scale based on findings from an examination of pelvic tenderness and induration (see section 7.2.2)
- Blood collection for central laboratory analysis of:
  - Endocrine parameters (prolactin, TSH and IGF-1)
  - Endometriosis biomarkers (VEGF, PlGF, IL-6, CA125 and sFlt-1)

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

- Access the IRT system to obtain an identification number for a vaginal ring to dispense
- Subject will be instructed to insert the assigned vaginal ring in the upper part of the vagina
- Supervision by the site staff can be provided if needed

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

- Inquiring bleeding pattern of the immediate past menstrual period (start / stop dates, amount)
- Recording of use of any concomitant medications including analgesics
- Recording of adverse events
- Dispensing of condoms and reminding the subject to use proper contraception
- Reminding the subject to attend the next visit, scheduled within 1-5 days of ring insertion

6.3 Treatment Period

If subjects do not have menstrual bleeding or have delayed menstrual bleeding in a cycle during the treatment period, a visit must be arranged within 35 days of the last ring replacement visit.

6.3.1 Visit 3 (Within 1-5 days of Visit 2)

Subjects will attend visit 3, scheduled within 1-5 days of visit 2.

The following must take place at the visit:

- Vital signs
- Blood collection for central laboratory analysis of
  - Endocrine parameters (prolactin, TSH and IGF-1)
  - Plasma concentrations of quinagolide and its metabolites
- Recording of use of any concomitant medications including analgesics
- Recording of adverse events
- Dispensing of condoms and reminding the subject to use proper contraception
- Reminding the subject to attend the next visit, scheduled within 7-14 days of ring insertion

6.3.2 Visit 4 (Within 7-14 days of Visit 2)

Subjects will attend visit 4, scheduled within 7-14 days of visit 2.

The following must take place at the visit:

- Blood collection for central laboratory analysis of
  - Plasma concentrations of quinagolide and its metabolites
- Recording of use of any concomitant medications including analgesics
- Recording of adverse events
- Dispensing of condoms and reminding the subject to use proper contraception
- Reminding the subject to attend the RM+7 visit of cycle 1

6.3.3 Cycle 1 Visit / Visit 5 (RM+7 of Cycle 1)

Subjects will attend visit 5, scheduled on RM+6-10 of cycle 1.

The following must take place before removal of the used ring and insertion of new ring:

- Ensuring the completion and legibility of NRS by the subject
- Urine pregnancy test [*note*: results must be negative]
- Blood collection for central laboratory analysis of:
  - Plasma concentrations of quinagolide and its metabolites

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

- Access the IRT system to obtain an identification number for a new vaginal ring to dispense
- Removal of the used ring and insertion of the new ring by the subject. Supervision by the site staff can be provided if needed
- Drug accountability of the ring
- Inquiring bleeding pattern of the immediate past menstrual period (start / stop dates, amount)
- Recording of use of any concomitant medications including analgesics
- Recording of adverse events
- Dispensing of condoms and reminding the subject to use proper contraception
- Reminding the subject to attend the RM+7 visit of cycle 2

6.3.4 Cycle 2 Visit / Visit 6 (RM+7 of Cycle 2)

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

The following must take place before removal of the used ring and insertion of new ring:

- Ensuring the completion and legibility of NRS by the subject
- Ensuring the completion and legibility of the EHP-30 questionnaire by the subject
- Urine pregnancy test [*note*: results must be negative. If positive, a serum βhCG test must be performed at the local laboratory]
- Blood collection for central laboratory analysis of:
  - Endocrine parameters (prolactin, TSH and IGF-1)
  - Plasma concentrations of quinagolide and its metabolites

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

- Access the IRT system to obtain an identification number for a new vaginal ring to dispense
- Removal of the used ring and insertion of the new ring by the subject. Supervision by the site staff can be provided if needed
- Drug accountability of the ring
- Inquiring bleeding pattern of the immediate past menstrual period (start / stop dates, amount)
- Recording of use of any concomitant medications including analgesics
- Recording of adverse events
- Dispensing of condoms and reminding the subject to use proper contraception
- Reminding the subject to attend the RM+7 visit of cycle 3

6.3.5 Cycle 3 Visit / Visit 7 (RM+7 of Cycle 3)

Subjects will attend cycle 3 visit (visit 7), scheduled on RM+6-10 of cycle 3.

The following must take place before removal of the used ring and insertion of new ring:

- Ensuring the completion and legibility of NRS by the subject
- Urine pregnancy test [*note*: results must be negative]
- Blood collection for central laboratory analysis of:
  - Plasma concentrations of quinagolide and its metabolites

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

- Access the IRT system to obtain an identification number for a new vaginal ring to dispense
- Removal of the used ring and insertion of the new ring by the subject. Supervision by the site staff can be provided if needed
- Drug accountability of the ring
- Inquiring bleeding pattern of the immediate past menstrual period (start / stop dates, amount)
- Recording of use of any concomitant medications including analgesics
- Recording of adverse events
- Dispensing of condoms and reminding the subject to use proper contraception
- Reminding the subject to attend the RM+7 visit of cycle 4

6.3.6 End-of-Treatment / Cycle 4 Visit / Visit 8 (RM+7 of Cycle 4)

If subjects attend all scheduled visits and complete the treatment, an end-of-treatment visit (visit 8) will be scheduled on RM+6-10 of cycle 4. If subjects are discontinued from the treatment prematurely, an end-of-treatment visit with the following end-of-treatment assessments should be scheduled within 2 weeks of discontinuation.

The following must take place first for all subjects:

- Ensuring the completion and legibility of NRS by the subject
- Ensuring the completion and legibility of the EHP-30 questionnaire by the subject
- Completing the first part of B&B scale based on the subject's verbal responses
- Urine pregnancy test [*note*: results must be negative]
- Blood collection for central laboratory analysis of:
  - Safety laboratory tests of clinical chemistry and haematology parameters
  - Endocrine parameters (prolactin, TSH and IGF-1)
  - Endometriosis biomarkers (VEGF, PlGF, IL-6, CA125 and sFlt-1)
  - Plasma concentrations of quinagolide and its metabolites

The subject will proceed to the following procedures after the above has been completed:

- Vital signs
- Physical examination
- Gynaecological examination
- Transvaginal ultrasound, preferably performed by the same sonographer as at screening (record the sizes of endometrioma / uterine fibroids, if any)
- Investigator completing the second part of B&B scale based on findings from an examination of pelvic tenderness and induration (see section 7.2.2)
- Removal of the used ring by the subject. Supervision by site staff can be provided if needed
- Drug accountability of the ring
- Inquiring bleeding pattern of the immediate past menstrual period (start / stop dates, amount)
- Recording of use of any concomitant medications including analgesics
- Recording of adverse events
- Completion of end-of-treatment form

Finally, for subjects who complete the treatment and subjects who are prematurely discontinued during or after cycle 2, the following must be performed at the site's affiliated radiology department:

- MRI examination [*note*: performed at or close to this visit when the subject has no bleeding and no ring. Fasting (no food or drink) for 3-4 hours in advance]

6.4 Follow-up

6.4.1 Follow-up Phone Call (About 1 Month after Visit 8)

A follow-up 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.

7 TRIAL ASSESSMENTS

7.1 Assessments Related to Primary Endpoint

7.1.1 Magnetic Resonance Imaging (MRI)

The MRI examination will be performed on a high resolution 3T machine at screening and at end-of-treatment / cycle 4. Depending on facilities at sites, MRI may not necessarily be scheduled at the RM+7 visit at screening or at cycle 4, but it must be scheduled on a day without bleeding close to the corresponding visits to avoid biases. 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. 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).

All the MRI machines will be cross-calibrated by a phantom to calibrate T1-T2 parameters for the DCE-MRI quantification. Calibration will be performed both prior to the trial initiation and in case of any software and hardware updates.

Subjects are required to fast for 3-4 hours before the MRI examination. The preparations for MRI examination should follow the 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 – 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. All images should be uploaded into a specific image repository allocated for this trial within 2 business days for central reading and analyses by the imaging laboratory. During image uploading, subjects' personal information (e.g. name) will be pseudonymised.

At screening, 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. The MRI used as baseline at screening should not be obtained more than 1 menstrual cycle before randomisation.

The central reading of MR images will be performed by two radiologists independently. In case of disagreement with regard to inclusion criterion no. 6, the opinion of a third radiologist will be sought and will determine the subject's eligibility. Based on the results of the central reading report, the investigators can decide which sub-group subjects belong to by allocating subjects to the more rare type in the ranking of DIE, adenomyosis and endometrioma. If one of the sub-groups has been fully enrolled, subjects will be allocated to the next rarer group.

The primary analyses will be based on measurable lesions (i.e. lesions with a size ≥10 mm) at baseline. All lesions with a size <10 mm will be identified as non-measurable lesions and the existence of such lesions will be recorded at baseline. All lesions, however, will be measured for the segmentation required in the analyses of the exploratory endpoints related to imaging biomarkers (section 7.3.1).

At end-of-treatment / cycle 4, all lesions will be compared to baseline to distinguish new lesion or disappearing lesion, defined as:

- New lesion: a lesion detected at end-of-treatment, regardless of its size, which is not detectable at baseline even during retrospective evaluations
- Disappearing lesion: a lesion detected at baseline, regardless of its size, which is not detectable at end-of-treatment

In case of any other incidental, clinically significant abnormal findings (e.g. suspected tumour) from MRI, it is the investigator's responsibility to inform subjects of the findings and to refer them to further examination and/or treatment. Such findings at end-of-treatment / cycle 4 should be reported as adverse events (section 8). If findings are serious (e.g. suspected malignant tumour), local radiologists and investigators are entitled to take prompt actions without waiting for central reading reports.

7.2 Assessments Related to Secondary Endpoints

7.2.1 Transvaginal Ultrasound (TVU)

Transvaginal ultrasound (TVU) will be performed, preferably by the same sonographer, at the screening visit and at end-of-treatment / cycle 4.

One purpose of TVU is to assess the general health status of uterus, endometrium and ovaries in order to identify any abnormal findings. The other purpose of TVU is to evaluate endometrial thickness, number and size of endometrioma if presented, number and size of fibroids if presented as well as number and size of ovarian cysts if presented.

Endometrial thickness (composed of both layers of the endometrium) will be measured in the sagittal view of the uterus from the proximal and distal interfaces between the echogenic

endometrium and the hypoechoic inner layer of the myometrium. Care should be taken not to include the presence of any fluid in the uterine cavity in calculating the endometrial thickness value. Endometrial thickness will be recorded in mm.

Endometrioma and/or fibroids will be recorded as observed or not. If observed, the number and size of endometrioma and/or fibroids should be recorded.

Ovarian cysts will also be recorded as observed or not. If observed, the number and size of ovarian cysts should be recorded.

7.2.2 Biberoglu and Behrman (B&B) Scale

B&B scale is a widely used scale for endometriosis that consists of two parts, with the first part evaluating symptoms (i.e. different types of pain) and the second part evaluating physical signs.

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

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

B&B will be administered on paper at randomisation and at end-of-treatment / cycle 4. Trial coordinators will complete the first part based on subjects' verbal response and the first part of the B&B should always be completed prior to ring insertion at randomisation and prior to other non-PRO procedures at end-of-treatment / cycle 4. Investigators will complete the second part of the B&B based on findings of a pelvic examination. The scores obtained at randomisation will be used as baseline.

To avoid bias in the assessment, the trial coordinator will only be able to access the first part of the scale for scoring while the investigator will only be able to access the second part of the scale. It is not allowed to have the same person administering both parts of the scale. The responses must be reviewed for legibility and completeness by the trial coordinator before the subject leaves the clinic. The B&B scale should be completed independently from the other PROs in this trial, i.e. without prior review of the NRS and EHP-30 scores completed by the subject.

7.2.3 Numerical Rating Scale (NRS)

NRS is a self-administered 11-point pain scale, with 0 indicating no pain and 10 indicating worst imaginable pain. At each RM+7 visits from randomisation to end-of-treatment / cycle 4, subjects will be asked to score the worst pain in relation to endometriosis / adenomyosis on the NRS based on a recall of their experiences during the following timeframes:

- during the last menstrual cycle
- during the menstrual period of the last menstrual cycle
- during the non-menstrual period of the last menstrual cycle

The NRS will be completed by subjects on paper prior to ring insertion at randomisation and prior to other non-PRO procedures at each RM+7 visit from cycle 1 to end-of-treatment / cycle 4. The responses must be reviewed for legibility and completeness by the trial coordinator before the subject leaves the clinic. The scores obtained at randomisation will be used as baseline.

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

The EHP-30 is a quality-of-life questionnaire specifically developed for endometriosis patients and is used in this trial for all subjects. Subjects will complete the core part of the EHP-30 questionnaire consisting of 30 questions measuring the frequency of the endometriosis impact on their quality of life during the past four weeks, with five options of never, rarely, sometimes, often and always.

EHP-30 will be completed on paper by subjects prior to ring insertion at randomisation, prior to other non-PRO procedures at cycle 2 and at end-of-treatment / cycle 4. The responses must be reviewed for legibility and completeness by the trial coordinator before the subject leaves the clinic. The scores obtained at randomisation will be used as baseline.

7.2.5 Menstrual Bleeding Pattern

At each RM+7 visit from randomisation to end-of-treatment / cycle 4, the site staff should inquire about the subject's immediate past menstrual period, including the start and stop dates (if available) of menstrual bleeding and the amount of menstrual flow. The amount of menstrual flow will be graded as none (no bleeding), mild (less than normal flow), moderate (normal flow) and heavy (more than normal flow).

7.2.6 Endocrine Parameters

Blood samples for measuring serum concentrations of prolactin, TSH and IGF-1 will be collected at randomisation, within 1-5 days of randomisation, at cycle 2 and at end-of-treatment / cycle 4.

The samples will be analysed at a central laboratory. However, the results of prolactin, TSH and IGF-1 after randomisation will be blinded to investigators, site staff and Ferring clinical team.

7.2.7 Plasma Concentrations of Quinagolide and Its Metabolites

Blood samples for measurement of plasma concentrations of quinagolide and its metabolites M1 and M2 will be collected within 1-5 days of randomisation, within 7-14 days of randomisation and at RM+7 visits of cycles 1 to 4. Blood samples should be taken prior to removal of the ring at RM+7 visits. The analysis of plasma concentrations of quinagolide and its metabolites will be performed by means of a validated tandem mass spectrometry method at a central laboratory.

7.2.8 Clinical Chemistry and Haematology Parameters

Blood samples for routine safety laboratory tests of clinical chemistry and haematology parameters (see lists below) will be drawn at the screening visit and at end-of-treatment / cycle 4. The samples will be analysed at a central laboratory.

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

Complete Blood Count: red blood cells, red blood cell morphology, white blood cells, white blood cell morphology, haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, platelets.

The investigator will review the laboratory results and evaluate and document whether the results are clinically significant or not. The laboratory report will be signed and dated by the investigator.

7.2.9 Adverse Events

Adverse events will be recorded from the signing of informed consent for participation in the trial until the end-of-trial. For each adverse event, the following parameters will be recorded by the investigator on the Adverse Event Log: description of event, date and time of onset, intensity, causal relation to IMP, action taken to IMP, other actions taken, seriousness of the adverse event, date and time of outcome, and outcome. See section 8.

7.3 Assessments Related to Exploratory Endpoints

7.3.1 MRI-Derived Perfusion and Diffusion Imaging Biomarkers

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 obtained at screening and at end-of-treatment / cycle 4. In order to convert the signal intensity to contrast concentration in every voxel, the GRE-T1 sequences acquired with different angles will be used to calculate the T1 value at every voxel by curve fitting. For the perfusion analysis, the different contrast enhancement curves will be obtained voxel-wise and a non-linear

least mean squares algorithm (Levenberg-Marquardt) will be used to extract the parameters of the model by curve fitting.

In addition, diffusion metrics (ADC, D, D* and f) of lesion tissue structure will be obtained using the IVIM model at screening and at end-of-treatment / cycle 4. For this purpose, the different curves of the signal intensity versus b-values will be obtained voxel-wise and a non-linear least mean squares algorithm (Levenberg-Marquardt) will be used to extract the parameters of the model by curve fitting. 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 measured for the analyses of the imaging biomarkers. Since the extraction of the parameters is performed voxel-wise, parametric maps will be generated in order to represent the parameters distribution in the different lesion regions.

7.3.2 Serum and Plasma Endometriosis Biomarkers

Blood samples will be taken at randomisation and at end-of-treatment / cycle 4 for the analysis of serum and plasma endometriosis biomarkers of VEGF, PlGF, IL-6, CA125 and sFlt-1. The samples will be analysed at a central laboratory.

All of the blood samples should be processed and stored in accordance with instructions provided in a separate laboratory manual. These exploratory data will be transferred to trial database directly.

7.4 Other Assessments

7.4.1 Demographics

Demographic information will be obtained at screening, including the following: date of birth (or partial date of birth per local regulations), ethnicity (Hispanic or Latino, Not Hispanic or Latino) and race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White).

7.4.2 Medical History

Any relevant medical history will be recorded at screening. This includes the year and method (e.g. laparoscopy) of endometriosis / adenomyosis diagnosis, documentation of a biopsy (if performed), stage of endometriosis at diagnosis (if available), anatomic location of lesions (if available), history of previous surgical interventions (including method [e.g. laparoscopy], year and type of surgery [ablation of lesions, excision of lesions, lysis of adhesions or other]), and any surgical intervention for other gynaecological conditions.

7.4.3 Menstrual History

Information about the menstrual history (average cycle length, average number of days with

menstrual bleeding and amount of menstrual flow) will be obtained at screening. In addition, the start and stop dates (if available) of the immediate past menstrual period should be noted. Any history of irregular vaginal bleeding outside menstrual period will also be recorded.

7.4.4 Reproductive History

Information about the reproductive history will be obtained at screening. This includes number of pregnancies, number of live births and history of infertility (yes/no and if yes, reason for infertility).

7.4.5 Body Measurement

Body weight and height will be measured without shoes at screening. The results obtained will be used to calculate BMI.

7.4.6 Urine Pregnancy Test

A urine pregnancy test will be performed at each clinic visit (except for visits 3 and 4) throughout the trial. The test should always be performed before ring insertion / removal at RM+7 visits of the treatment periods. If the urine test result is positive, blood collection for βhCG test at the local laboratory must be performed. If both test results are positive, the subject will be discontinued from the trial.

7.4.7 Vital Signs

Systolic and diastolic blood pressure as well as pulse will be measured at the screening visit, prior to randomisation at the randomisation visit, within 1-5 days of the first ring insertion (i.e. visit 3) and at end-of-treatment / cycle 4. Vital signs at randomisation will be baseline. Blood pressure and pulse should be measured by automated oscillometric device sequentially, first after the subject is in supine position for at least 3 minutes, then in seated position for at least 3 minutes, and then at 1 minute and at 3 minutes after standing. Changes in blood pressure will be calculated using the minimum standing measurement minus the seated measurement and minus the supine measurement, respectively. A drop of 20 mmHg of systolic blood pressure or a drop of 10 mmHg of diastolic blood pressure from lying to standing or from sitting to standing is considered clinically significant.

The investigator will review the results of vital signs and evaluate and document whether the finding is clinically significant or not. Any clinically significant finding will be reported as medical history (if reported at screening) or as adverse events (if reported during the treatment).

7.4.8 Physical Examination

A complete physical examination will be performed at the screening visit and at end-of-treatment / cycle 4. Information will be recorded for general appearance, central and peripheral nervous

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

Each category will be evaluated as normal, abnormal not clinically significant or abnormal clinically significant. Abnormal clinically significant findings at the screening visit (baseline) must be reported on the Medical History Log.

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

7.4.9 Gynaecological Examination

A gynaecological examination will be performed by the investigator at the screening visit and at end-of-treatment / cycle 4. Information will be recorded for breast, external genitalia, vagina, cervix, uterus, uterine adnexa (including ovaries and fallopian tubes) and cul-de-sac.

Each category will be evaluated as normal, abnormal not clinically significant or abnormal clinically significant. Abnormal clinically significant findings at the screening visit (baseline) must be reported on the Medical History Log.

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

7.4.10 Cervical Cytology Test

As part of eligibility check, a cervical cytology test using a liquid-based method will be performed at the screening visit for subjects who do not have a cervical cytology test within 24 months of the visit. If there is any presence of atypical squamous cells of undetermined significance, a reflex testing for HPV must be performed. Subjects with positive HPV test results must be excluded. In case of positive findings, it is the investigator's responsibility to ensure that standard reporting and referral procedures at the sites are followed in line with local regulations.

7.4.11 Concomitant Medications

The use of any hormonal treatment of endometriosis and/or adenomyosis within the last 6 months prior to the signing of the informed consent for participation in the trial will be recorded. The use of any other concomitant medications within the last 3 months prior to informed consent for

participation in the trial and throughout the trial will be recorded. Recording of concomitant medications will be performed at all visits.

Any use of analgesics, including the dose and the frequency, will be collected in the e-CRF.

7.4.12 Drug Accountability

For all vaginal rings, date and time of insertion and removal at the clinics will be recorded in the IRT system. Any incidents of ring out of the body for more than 24 hours should be captured in the e-CRF.

7.4.13 End-of-Treatment Form

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

7.4.14 Follow-up Phone Call

A follow-up 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.

7.5 Handling of Biological Samples

Trial-specific laboratory manuals will be provided to the participating sites, describing in detail how to handle, store and transport the biological samples (blood) in this trial. All blood samples collected during the trial will be analysed at central laboratories and will be destroyed within 2 years after reporting of the trial. For all biological samples collected in the trial, it applies that any analyses beyond those described in the protocol will be performed only after obtaining the required approvals. The processes related to handling of biological samples will be described in the informed consent form, and the biobank / data protection legislations including local legislation will be adhered to.

8 ADVERSE EVENTS

8.1 Adverse Event Definition

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

- Any unfavourable and unintended sign, symptom or disease temporally associated with the use of the IMP, whether or not considered to be caused by the IMP.
- Adverse events commonly observed and adverse events anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality, vital sign or finding from physical or gynaecological examination assessed as clinically significant by the investigator [*note*: pre-existing conditions diagnosed through assessments and examinations at the screening visit or during the screening period are not adverse events, but are recorded as medical history.]
- Accidental injuries, reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures.

All adverse events will be coded by Ferring Pharmacovigilance using Medical Dictionary for Regulatory Activities (MedDRA).

Medication errors of IMP will be captured in the e-CRF and will be reviewed by Ferring Pharmacovigilance on an ongoing basis.

8.2 Collection and Recording of Adverse Events

8.2.1 Collection of Adverse Events

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

The sources of adverse events cover:

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

8.2.2 Recording of Adverse Events

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

- Adverse event
- Date and time of onset
- Intensity
- Causal relationship to IMP
- Action taken to IMP
- Other action taken
- Date and time of outcome
- Outcome
- Seriousness

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

Adverse Event

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

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

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

Date and Time of Onset

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

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

Intensity

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

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

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

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

Causal Relationship to IMP

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

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

Examples:

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

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

Examples:

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

Action Taken to IMP

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

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

Other Action Taken

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

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

Date and Time of Outcome

The date and time the subject recovered or died.

Outcome

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

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

8.3 Adverse Events of Special Interest

8.3.1 Dysmenorrhea, Pelvic Pain and Dyspareunia

Presence of dysmenorrhea, pelvic pain and dyspareunia related to endometriosis / adenomyosis will be assessed by B&B and NRS as part of the secondary endpoints and therefore is not to be reported as an adverse event unless it fulfils the criteria for a serious adverse event (SAE).

8.3.2 Menstrual Bleeding

Presence of abnormal menstrual bleeding (e.g. amenorrhea, oligomenorrhea and menorrhagia) will be assessed by menstrual pattern at each RM+7 visit from randomisation to end-of-treatment / cycle 4 as part of the secondary endpoints and therefore is not to be reported as an adverse event unless it fulfils the criteria for an SAE.

8.4 Pregnancy and Pregnancy Outcome

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

8.5 Serious Adverse Events

8.5.1 Serious Adverse Event Definition

Serious Adverse Events during the Trial

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

8.5.2 Collection, Recording and Reporting of Serious Adverse Events

SAE Reporting by the Investigator

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

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

SAE Report Form

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

Global Pharmacovigilance, Ferring Pharmaceuticals A/S
E-mail: [redacted]
Fax: [redacted]

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

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

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

Expedited Reporting by Ferring

Ferring will report all adverse events that are **serious, unexpected and with a reasonable possible causality to the IMP** as judged by either the investigator or Ferring to the relevant parties within the stipulated timelines.

The expectedness is assessed by Ferring according to the Investigator's Brochure.[15]

SAEs will be considered reportable regardless of whether or not the IMP was used in accordance with the provisions in the protocol, Investigator's Brochure[15] and labelling.

8.6 Follow-up of Adverse Events and Serious Adverse Events

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

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

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

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

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

9 STATISTICAL METHODS

This section details the planned statistical analysis of the primary endpoints and outlines the planned statistical analysis for the secondary endpoints. All analyses and further description of the statistical methodology for primary as well as secondary endpoints will be included in the statistical analysis plan (SAP). The SAP will be available before breaking the blind.

9.1 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,[39] 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 9-1 summarises the required sample size in total for different assumptions of treatment effect difference and power.

Table 9-1 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.

9.2 Subject Disposition

All subjects screened and randomised will be accounted for. Screened subjects who discontinue from the trial prior to randomisation are regarded as screening failures. The number of screened but not randomised subjects will be summarised by primary reason for screening failure.

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

All premature discontinuations will be summarised and listed by time of and reason for discontinuation. The treatment group difference in the proportion of subjects who discontinue will be tested using the Fishers exact test.

9.3 Protocol Deviations

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

- Treatment received not in accordance with randomisation
- Non-compliance with IMP treatment regimen for >20% of days during the non-menstrual period

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

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

9.4 Analysis Sets

9.4.1 Full Analysis Set (FAS)

The FAS comprises all randomised and treated subjects and is analysed according to the planned treatment.

9.4.2 Per Protocol (PP) Analysis Set

The PP analysis set is defined as all randomised subjects except those with a major protocol deviations as described in section 9.3.

9.4.3 Safety Analysis Set

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

9.5 Trial Population

9.5.1 Demographics and other Baseline Characteristics

All relevant baseline data will be summarised in tables by treatment groups and in total. In addition summary tables will be presented by trial site.

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

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

9.5.2 Medical History, Concomitant Medication and Other Safety Evaluations

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

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

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

9.6 Endpoint Assessments

9.6.1 General Considerations

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

The analysis of all the secondary and exploratory endpoints except the safety endpoints (i.e. adverse events, clinical chemistry and haematology parameters) will be performed for the FAS population. The safety endpoints will be analysed for the safety analysis set unless otherwise noted.

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

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

Missing Data

Missing data from the MRI
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.

If the end-of-treatment MRI examination is not performed or is missing, the missing measurement will be imputed using a multiple imputation strategy. The imputation will be based on a missing-at-random assumption using baseline MRI results and some other measurements. The precise imputation strategy will be described in the SAP.

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

9.6.2 Primary Endpoint

For each type of lesion (endometrioma, DIE and adenomyosis), the primary endpoint is the change in the sum of the lesion sizes at cycle 4, 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 cycle 4. 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.

For each type of lesions, 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 cycle 4 as the dependent variable, the baseline sum of lesions as covariate, the treatment group and site as fixed effect. The treatment difference between active treatment versus placebo will be reported with 95% confidence interval and corresponding p-value for each of the three types of lesions:

$$\begin{cases} H_0^{P1}: & \mu_{QVR}^1 = \mu_{Placebo}^1 \\ H_1^{P1}: & \mu_{QVR}^1 \neq \mu_{Placebo}^1 \end{cases}$$

$$\begin{cases} H_0^{P2}: & \mu_{QVR}^2 = \mu_{Placebo}^2 \\ H_1^{P2}: & \mu_{QVR}^2 \neq \mu_{Placebo}^2 \end{cases}$$

$$\begin{cases} H_0^{P3}: & \mu_{QVR}^3 = \mu_{Placebo}^3 \\ H_1^{P3}: & \mu_{QVR}^3 \neq \mu_{Placebo}^3 \end{cases}$$

Where $(H_0^{P1}), (H_0^{P2}), (H_0^{P3})$ are the null hypotheses for each of the 3 types of lesions, $(H_1^{P1}), (H_1^{P2})$, (H_1^{P3}) are the alternative hypotheses for each of the 3 types of lesions, and

$$\begin{cases} \mu_{QVR}^1 = \text{The mean change from baseline in the sum of the size of the endomitrioma lesions at cycle 4 for QVR} \\ \mu_{QVR}^2 = \text{The mean change from baseline in the sum of the size of the DIE lesions at cycle 4 for QVR} \\ \mu_{QVR}^3 = \text{The mean change from baseline in the sum of the size of the adenomyosis lesions at cycle 4 for QVR} \\ \mu_{placebo}^1 = \text{The mean change from baseline in the sum of the size of the endomitrioma lesions at cycle 4 for placebo ring} \\ \mu_{placebo}^2 = \text{The mean change from baseline in the sum of the size of the DIE lesions at cycle 4 for placebo ring} \\ \mu_{placebo}^3 = \text{The mean change from baseline in the sum of the size of the adenomyosis lesions at cycle 4 for placebo ring} \end{cases}$$

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.

The primary analysis is based on the FAS including those missing the end-of-treatment MRI results. As described above, missing values will be imputed using a multiple imputation strategy.

Sensitivity Analyses

The following sensitivity analyses will be conducted:

1. To test efficacy in more perfect conditions:
   - The primary analysis in the PP population
2. To test sensitivity to missing data:
   - The primary analysis performed on completers (defined as subjects who have completed the scheduled treatment and have both a baseline and a cycle 4 MRI)
   - The primary analysis performed on subjects with both a baseline and an end-of-treatment MRI
   - The FAS using multiple imputation for missing data in a placebo-based pattern mixture model (based on a missing-not-at-random condition) as described by Ratitch

3. The primary analysis using the actual treatment rather than the planned treatment
4. The primary analysis using also lesions that are <10 mm at baseline
5. The primary analysis adjusted for the type of previous hormonal treatment

9.6.3 Secondary Endpoints

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

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

Count data related to the number of new / disappearing lesions by type, based on all lesions, will be analysed with repeated measures negative-binomial regression using a GEE approach. The regression analysis will be performed with log link function using the appropriate off-set.

Changes from baseline in the volume of endometrioma/DIE lesions assessed by MRI at cycle 4 and in the sizes of endometrioma assessed by TVU at cycle 4 will be analysed similarly to the primary endpoint, but sensitivity analyses will not be performed for these secondary endpoints.

Secondary endpoints related to PROs (B&B, NRS and EHP-30) and endocrine parameters 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 by time as fixed effect. The error-covariance matrix will be unstructured.

Changes in the menstrual bleeding pattern will be analysed by investigating the time to first event of change in bleeding pattern using the proportional odds regression model.

Plasma concentration of quinagolide and its metabolites will be analysed descriptively. 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.

All analyses and respective definitions of the endpoints will be further detailed in the SAP.

9.6.4 Exploratory Endpoints

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.

Changes in the sizes of uterine fibroids assessed by MRI / TVU and changes in the plasma and serum endometriosis biomarkers will be analysed in a similar way as the primary endpoint but without sensitivity analyses.

9.7 Extent of Exposure and Treatment Compliance

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

9.8 Safety

General Considerations

This section describes the descriptive analyses of safety endpoints and routine safety assessments. The safety endpoints described in this section will be analysed for the safety analysis set.

Clinical Chemistry and Haematology Parameters

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

Adverse Events

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

Summary tables will be prepared for the following: all adverse events, adverse events by causality (reasonable possibility / no reasonable possibility), adverse events leading to death, adverse events by intensity (mild / moderate/ severe), adverse reactions by intensity (mild / moderate/ severe), SAEs, adverse events leading to discontinuation, adverse events with an incidence of at least 5% in any treatment group, non-SAEs with an incidence of at least 5% in any treatment group. A separate data listing will be provided for pre-treatment adverse events.[d]

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

[c] 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.

[d] 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.

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

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

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

Other Safety Variables

Vital Signs

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

Physical and Gynaecological Examination

Physical and gynaecological examination findings at cycle 4 / end-of-treatment compared to screening will be summarised in shift tables and all subjects with any abnormal finding will be listed by subject and time point. The list will include both screening and cycle 4 / end-of-treatment assessment for comparison.

9.9 Interim Analysis

No interim analysis is planned for this trial.

10 DATA HANDLING

10.1 Source Data and Source Documents

Source Data – ICH Definition

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

Source Documents - ICH Definition

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

Trial-specific Source Data Requirements – Ferring

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

- Existence of subject (initials, date of birth)
- Confirmation of participation in trial (trial ID, subject ID)
- Informed consent (date and time of oral information, date and time of handing out informed consent form, date and time of obtaining signed informed consent)
- Eligibility for participation in the trial (documenting all inclusion / exclusion criteria)
- Relevant medical history
- Visit dates
- MR images
- Dates of insertion/removal of the ring
- Dates and indication of concomitant medications
- PROs (B&B, NRS and EHP-30)
- Adverse events (description as well as start/stop date and time)
- Reason for discontinuation
- Event of unblinding, including the reason for unblinding

The source data for the MRI evaluation will be located at the central imaging laboratory. The source data for the endocrine parameters, clinical chemistry and haematology parameters will be

available at the central laboratory during the trial.

10.2 e-CRF

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

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

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

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

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

10.3 Data Management

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

10.4 Provision of Additional Information

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

11 MONITORING PROCEDURES

11.1 Periodic Monitoring

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

The investigator / radiologist will permit the monitor direct access to all source data, including MR images, electronic medical records, and/or documents in order to facilitate data verification. The investigator will cooperate with the monitor to ensure that any discrepancies that may be identified are resolved. The investigator is expected to be able to meet the monitor during these visits. When the first subject is randomised at the trial site, a monitoring visit will take place shortly afterwards. For this trial, the frequency of the monitoring visits per site will be determined through a risk-based approach depending on recruitment rate, observed data quality and overall site performance.

The source data for central evaluation of MR images will also be verified, and monitoring visits to the central reading laboratory will take place on a regular basis during the trial.

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

11.2 Audit and Inspection

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

The main purposes of an audit or inspection are to assess compliance with the trial protocol and the principles of ICH-GCP including the Declaration of Helsinki,[44] and all other relevant regulations.

The subjects must be informed by the investigator and in the informed consent form that authorised Ferring representatives and representatives from regulatory authorities and IECs may wish to inspect their medical records. During audits/inspections, the auditors/inspectors may copy relevant parts of the medical records. No personal identification apart from the screening / randomisation number will appear on these copies.

The investigator should notify Ferring without any delay of any inspection by a regulatory authority or IEC.

11.3 Confidentiality of Subject Data

The investigator will ensure that the confidentiality of the subjects' data will be preserved. In the e-CRF or any other documents submitted to Ferring, the subjects will not be identified by their names, but by an identification system, which consists of an assigned number in the trial. Documents that are not for submission to Ferring, e.g. the confidential subject identification code and the signed informed consent form, will be maintained by the investigator in strict confidence.

12 CHANGES IN THE CONDUCT OF THE TRIAL

12.1 Protocol Amendments

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

12.2 Deviations from the Protocol

Deviations from the protocol should not occur. If deviations occur, the investigator must inform the monitor, and the implications of the deviation must be reviewed and discussed. Any deviation must be documented, either as answer to a query in the e-CRF, in a protocol deviation report or a combination of both. A log of protocol deviation reports will be maintained by Ferring. Protocol deviation reports and supporting documentation must be kept in the Investigator's File and in the Trial Master File.

12.3 Premature Trial Termination

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

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

13 REPORTING AND PUBLICATION

13.1 Clinical Trial Report

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

13.2 Confidentiality and Ownership of Trial Data

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

13.3 Publications and Public Disclosure

13.3.1 Publication Policy

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

Authorship is granted based on the criteria established by the International Committee of Medical Journal Editors (ICMJE).[45] The total number of authors is based on the guideline from the relevant journal or congress. In the event of any disagreement in the content of a publication, both the investigator's and Ferring's opinion will be fairly and sufficiently represented in the publication.

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

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

13.3.2 Public Disclosure Policy

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

14 ETHICAL AND REGULATORY ASPECTS

14.1 Independent Ethics Committee (IEC)

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

14.2 Regulatory Authorities' Notification

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

14.3 End-of-Trial and End-of-Trial Notification

The end of the trial is defined as the date of approximately 1 month after LPLV, i.e. when the follow-up phone call is made.

At the end of the trial, the sponsor shall notify the regulatory authorities and the IECs in the participating countries about the completion of the clinical trial within 90 days when the trial has ended in all countries.

In the case of early termination, Ferring must notify the end of the trial to the national regulatory authorities and the IECs immediately and at the latest within 15 days after the trial is halted, clearly explain the reasons, and describe follow-up measures, if any, taken for safety reasons.

Within one year of the end of the trial, Ferring shall send a summary of the final Clinical Trial Report to the national regulatory authorities and the IECs.

14.4 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki,[44] in compliance with the approved protocol, ICH-GCP and applicable regulatory requirements.

14.5 Informed Consent

The investigator (or the person delegated by the investigator) will obtain a freely given written consent from each subject after an appropriate explanation of the aims, methods, sources of funding, any possible conflicts of interest, anticipated benefits, potential hazards, and any other aspects of the trial which are relevant to the subject's decision to participate. The trial subject must be given ample time to consider participation in the trial, before the consent is obtained. The

informed consent form must be signed and dated by the subject and the investigator who has provided information to the subject regarding the trial before the subject is exposed to any trial-related procedure, including screening tests for eligibility. Subjects must be given the option of being informed about the general outcome and the results of the trial.

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

The subject will receive a signed copy of the Informed Consent Form before any trial-related procedures.

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

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

14.6 Subject Participation Card

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

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

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

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

14.7 Compliance Reference Documents

The Declaration of Helsinki,[44] the consolidated ICH-GCP, the EU Clinical Trials Directive and other national laws in the countries where the trial takes place shall constitute the main reference guidelines for ethical and regulatory conduct.

15 LIABILITIES AND INSURANCE

15.1 ICH-GCP Responsibilities

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

15.2 Liabilities and Insurance

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

16 ARCHIVING

16.1 Investigator File

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

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

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

16.2 Trial Master File

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

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