COVANCE

Ipsen Pharma

Protocol No.: D-CN-52014-220

A Phase III, Multicentre, Randomised, Open-label, Parallel, Active-controlled Study to Compare the Oestradiol Suppression, Clinical Efficacy and Safety of Two Formulations of Triptorelin (Triptorelin Pamoate PR 3-month and Triptorelin Acetate PR 1-month) in Chinese Subjects with Endometriosis

CCI [redacted]

STATISTICAL ANALYSIS PLAN

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APPROVALS

The undersigned agree that all required reviews of this document are complete, and approve this <DMC> Statistical Analysis Plan as final. Programming of the tables, figures and listings based upon the specifications within this document can proceed.

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REVIEWERS

The following reviews of the SAP were conducted:

Name	Role	Version Last Reviewed	Company/ Organisation
PPD	PPD	Final 1.1	Ipsen
PPD	PPD	Draft 1.1	Ipsen
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PPD	PPD	Final 1.1	Ipsen
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PPD	PPD	Final 1.1	Ipsen
PPD	PPD	Final 1.1	Ipsen
PPD	PPD	Draft 1.1	Ipsen
PPD	PPD	Draft 1.1	Ipsen
PPD	PPD	Final 1.1	Covance
PPD	PPD	Draft 1.0	Covance
PPD	PPD	Final 1.1	Covance
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PPD	PPD	Final 1.1	Covance
PPD	PPD	Final 1.1	Covance

VERSION HISTORY

Version Number	Version Date	Summary and rational of change(s)
Final 1.0	July 11, 2017	First final version.
Final 2.0 (amendment 1.0)	February 01, 2018	1. Based on the new version of protocol, the following sections are updated: 1) Section 3.1 Primary Efficacy Endpoint: delete "blinded"; 2) Section 7.6.2 Secondary Efficacy Analysis: use "last dose" instead of "first dose" in definition of time to menses; 3) Section 7.7.3 Electrocardiograms: delete RR intervals and delete QTcF accordingly calculated from RR; 2. Based on the new version of CRF, the following sections are updated: 1) Section 7.7.1 Adverse Event: delete the sentence "AE with multiple episodes will be counted as one AE when calculating number of events.", because one AE will be collected in one record (no multiple episodes); 3. Delete TFL index in Appendix II, in order to update/maintain a separate file of TFL mockup.
Final 3.0		1. Update based on findings from the first dry run. 1) Include a new Section 6.2.1 Handling of triptorelin BLO concentration values (Full PK/PD subgroup) to specify how BLQ will be handled when perform statistical summary. 2) Section 7.3 Protocol Deviations: all PD should be listed. A new major PD listing to be provided with flagging on PDs affects on efficacy and/or PK/PD variables. 3) Section 7.6.2 Secondary Efficacy Analysis – Time to Menses Recovery: Additional description on how to handle subjects whose menses didn't stop before last dose. 4) Section 7.7.1 Adverse Events: Replace "Pre-dosing adverse events" to "Non-TEAE". 5) Section 7.7.2 Laboratory Evaluations: Update Table 2 PCSA Criteria for Laboratory Tests. 6) Section 7.7.3 Electrocardiograms: Update Table 3 PCSA Criteria for ECG. 7) Section 7.7.4 Vital Signs: Include normal range for vital signs.

		2. Section 7.8 Pharmacokinetics: Additional imputation provided by Ipsen.
Final 3.1		1) Add criterion "with primary endpoint measurement at week 12" in the definition of PP set, as for subjects without primary endpoint measurement at week 12, some reported PD, while some not. 2) Section 7.3 Protocol Deviations: "Major protocol deviations affecting efficacy endpoints leading to exclusion from the PP set" replaced by "Major protocol deviations affecting primary efficacy endpoint leading to exclusion from the PP set". 3) Section 7.6.2 Secondary Efficacy Analysis – Time to Menses Recovery: "before last dose" replaced by "during the treatment duration (V2 till V8)".

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BLQ	Below the Limit of Quantification
CI	Confidence Interval
E_2	Oestradiol
ECG	Electrocardiogram
eCRF	Electronic case report form
FAS	Full Analysis Set
FSH	Follicle stimulating hormone
ICH	International Conference on Harmonization
IMP	Investigational medicinal product
LH	Luteinising hormone
MedDRA	Medical Dictionary for Regulatory Activities
n	Number of available observations
PCSA	Potentially clinically significant abnormalities
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per protocol
PR	Prolonged release
PT	Preferred term
QTcF	Fridericia corrected QT interval
RBC	Red blood cell(s)
SAP	Statistical analysis plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
VAS	Visual analogue scale
WBC	White blood cell(s)

1 SOURCE DOCUMENTS

This Statistical Analysis Plan (SAP) was written based on the following documents:

- Protocol final version 3.0 (Amendment 2.0), dated on 29 September 2017
- Electronic case report forms (eCRF) version 2.00, dated on 29 November 2017
- International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" [1]
- ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports" [2]

2 PROTOCOL DETAILS

2.1 Study Objectives

The primary objective of the study is to assess the efficacy of triptorelin pamoate prolonged release (PR) 3-month formulation in Chinese female subjects with endometriosis by demonstrating the noninferiority of triptorelin pamoate PR 3-month formulation injected once as compared to triptorelin acetate PR 1-month formulation injected 3 times consecutively, assessed by the percentage of subjects castrated (oestradiol (E_2)≤184 pmol/L or 50 pg/mL) at Week 12.

The secondary objectives of the study are as follows:

- To assess other efficacy parameters including the percentage of subjects castrated at other time points, E_2, lutenising hormone (LH), and follicle stimulating hormone (FSH) concentrations, and the impact on endometriosis-associated pelvic pain.
- To assess the safety profile of triptorelin pamoate PR 3-month.
- To assess the pharmacokinetics (PK) of triptorelin pamoate PR 3-month and compare to triptorelin acetate PR 1-month.

The exploratory objectives of the study are:

- To assess other efficacy parameters (percentage of subjects castrated, E_2, LH and FSH concentrations and the impact on endometriosis-associated pelvic pain) after Week 12.
- To explore the PK/ pharmacodynamic (PD) relationship of triptorelin pamoate PR 3-month in a subset of subjects (PD markers being E_2, FSH and LH).

2.2 Overall Study Design

This prospective, Phase III, multicentre, randomised, open-label, parallel group, active-controlled study will compare triptorelin pamoate PR 3-month with triptorelin acetate PR 1-month for the treatment of Chinese female subjects with endometriosis.

Subjects with endometriosis will be screened for eligibility up to 5 weeks prior to the first dose of investigational medicinal product (IMP), which must occur during the follicular phase of the menstrual cycle. A total of 300 eligible subjects will be stratified by endometriotic surgical history (previous vs. no previous surgery) and the severity of endometriosis-associated pelvic pain (assessed by a visual analogue scale (VAS): VAS>3 or ≤3 cm) and randomised in a 1:1 ratio to receive either triptorelin pamoate PR 3-

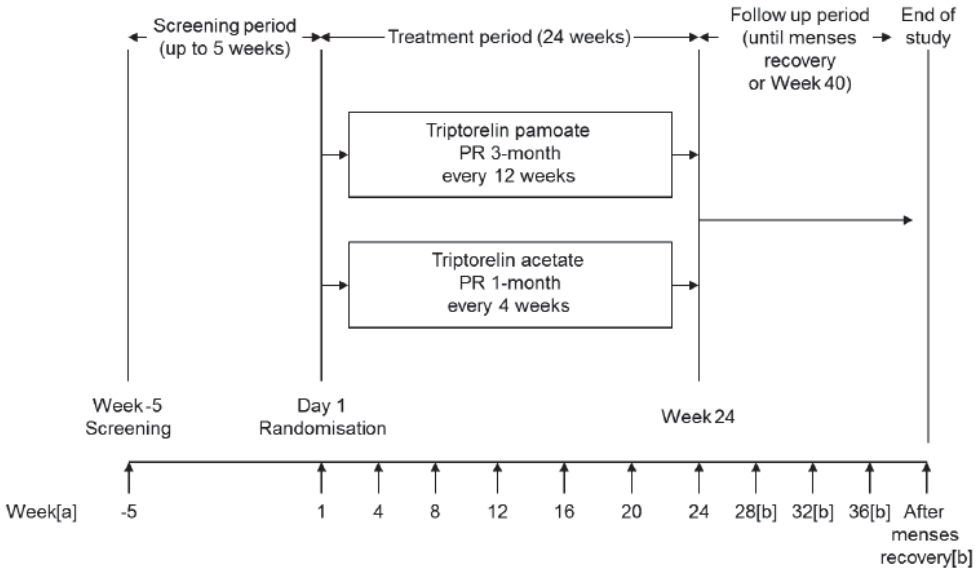
month once per 12 weeks (total 2 injections, one each at baseline and Week 12) or triptorelin acetate PR 1-month once per 4 weeks (total 6 injections, one each at baseline and Week 4, 8, 12, 16 and 20) for a 24-week treatment phase.

All subjects will visit the study site every 4 weeks until Week 24. The subgroup participating in the full PK and exploratory PD evaluations (up to 32 subjects, 16 from each treatment group, enrolled at the selected site) will have additional study visits during the treatment phase. If needed in the opinion of investigator, "add back" treatment (recommended as, but not limited to, tibolone at a dose of 2.5 mg once daily) may be applied from Week 12. After 24 weeks' study treatment, subjects receiving triptorelin pamoate PR 3-month and participating in the full PK/PD subgroup will visit the study site, and other subjects will be followed up by telephone every 4 weeks until menses recovery or Week 40 (whichever is earlier). All subjects will attend the study site for the end of study visit (the first visit after menses recovery, or Week 40).

This study will consist of a screening period of up to 5 weeks, a 24-week open-label treatment period and a follow up period of up to 16 weeks. The duration of the study is a minimum of 24 to 40 weeks, plus up to 5 weeks for the screening period.

The principal study design features are summarised in Figure 1. The scheduled events at every visit are summarised in Table 5 (all subjects) and Table 6 (PK/PD subgroup subjects).

Figure 1 Study Design



[a] additional visits for subjects in the PK/PD subgroups not indicated
[b] during follow up, the first visit after menses recovery, or Week 40 (whichever is earlier) is considered the end of study visit

2.3 Sample Size and Power

The sample size was estimated based on data from Ipsen Study E-28-52014-705. Assuming the percentage of subjects castrated at Week 12 of triptorelin acetate PR 1-month treatment is no less than 92%, a sample size of 133 subjects in each treatment group will have 85% power to demonstrate the noninferiority of

triptorelin pamoate PR 3-month to the comparator, when the lower limit of the 95% confidence interval (CI) of the difference in percentage of subjects castrated at Week 12 between the treatment groups is ≥-10% and with a 0.025 one-sided type I error rate.

Assuming that the dropout rate will be around 10%, a sample size of 300 randomised subjects in total is planned for this study.

3 EFFICACY AND SAFETY VARIABLES

3.1 Primary Efficacy Endpoint(s)

The percentage of subjects castrated (E_2 ≤184 pmol/L or 50 pg/mL) at Week 12. The primary endpoint will be evaluated on centralised bioanalysis of serum samples for E_2.

3.2 Secondary Efficacy Endpoints

The secondary endpoints for this study include:

- Percentage of subjects castrated (E_2 ≤184 pmol/L or 50 pg/mL) at Weeks 4 and 8.
- Percentage of subjects castrated (E_2 ≤110 pmol/L or 30 pg/mL) at Weeks 4, 8 and 12.
- Change in endometriosis-associated pelvic pain (by 10 cm VAS) at Weeks 4, 8 and 12 compared to baseline.
- E_2, FSH and LH concentrations at Weeks 4, 8 and 12.
- Time to menses recovery.

3.3 Exploratory Efficacy Endpoints

The exploratory endpoints for this study include:

- Percentage of subjects castrated (as defined by both E_2 ≤184 pmol/L (50 pg/mL) and E_2 ≤ 110 pmol/L (30 pg/mL)) at Week 24.
- Change in endometriosis-associated pelvic pain (by 10cm VAS) at Weeks 16, 20 and 24 and the end of study visit compared to baseline.
- Concentrations of E_2, FSH and LH at Week 24.
- The PK/PD relationship will be explored (PD markers: E_2, FSH and LH) for triptorelin acetate PR 1-month formulation and triptorelin pamoate PR 3-month formulation.

3.4 Safety Variables

The safety and tolerability of triptorelin will be assessed by evaluating as follows:

- Adverse events (AEs) throughout the study,
- Clinical laboratory parameters (biochemistry, haematology and urinalysis) test results at screening, Weeks 12 and 24,
- Electrocardiogram (ECG) findings at screening, Weeks 12 and 24,
- Serum hormone (E_2, FSH and LH) concentrations at Week 40 (for those subjects whose menses do not recover at Week 40),

- Vital signs (blood pressure and heart rate) measurements at each visit during treatment and end of study visit,
- Physical/pelvic examination at screening, Weeks 12 and 24,
- Pelvic type B ultrasound at screening (or within 1 month prior to screening), Week 12 (optional) and Week 24,
- Urinary pregnancy test at screening and baseline visit.

4 PHARMACOKINETIC VARIABLES

A full triptorelin PK characterisation, using a non-compartmental analysis (NCA) approach, will be conducted in a subgroup of up to 16 subjects in each treatment group to be enrolled at selected sites. PK parameters (C_{min}, C_{max}, t_{max} and AUC_{tau} where applicable) will be calculated for triptorelin acetate PR-1 month after the first administration and triptorelin pamoate PR 3-month after the first and last administration.

5 ANALYSIS SETS

5.1 Screened Set

All subjects screened (i.e. who signed the informed consent) are included in Screened set.

5.2 Randomised Set

All subjects randomised (i.e. who were randomly allocated to a treatment group) are included in the Randomised Set.

Randomised subjects are analysed according to their assigned treatment.

5.3 Safety Set

The Safety Set includes all subjects who received at least one dose of study medication.

The Safety Set will be used for safety analyses according to the actual treatment received for each subject.

5.4 Full Analysis Set (FAS)

The full analysis set (FAS) includes all randomised subjects who received at least one dose of study medication with at least one baseline and at least one post-baseline assessment of the primary efficacy parameter.

The FAS will be used to analyse primary and secondary efficacy endpoints. All exploratory efficacy endpoints will be performed on the FAS.

FAS subjects are analysed according to their randomised treatment.

5.5 Per Protocol (PP) Set

The per protocol (PP) set includes all subjects in the FAS with primary endpoint measurement at week 12, and without major protocol violations/deviations affecting primary efficacy endpoint.

Major protocol deviations are those that affect the primary efficacy endpoint and the criteria of major protocol deviations will be defined in the file of protocol deviation document. The process to review major

protocol deviations will be ongoing and the final PP subjects will be determined during the data review meeting held prior to database lock.

The PP set will be used to analyse primary and secondary efficacy endpoints.

The PP set will be the primary analysis population for the primary efficacy endpoint.

5.6 Full PK Profile Analysis Set

The Full PK Profile Analysis Set includes subjects in the full PK/PD subgroup who receive at least one dose of IMP, have no major protocol deviations affecting the PK variables, and have a sufficient number of PK concentration measurements to estimate the main PK parameters: maximum observed plasma concentration (C_{max}) and time to maximum observed plasma concentration (t_{max}), and area under the plasma concentration-time curve for the dosing interval (AUC_{tau}) where applicable.

The criteria of Major protocol deviations affecting the PK variables will be defined in the protocol deviation document. The process to review major protocol deviations potential impact on PK parameters will be ongoing and the final Full PK Profile Analysis Set will be determined during data review meeting.

The Full PK Profile Analysis Set will be used for PK parameter analyses using an NCA approach. The detailed PK analysis methodology will be included in a separate PK analysis plan.

5.7 Sparse PK Sampling Analysis Set

The Sparse PK Sampling Analysis Set includes all subjects who receive at least one dose of IMP, have no major protocol deviations affecting the PK variables and have at least one valid plasma concentration.

The criteria of Major protocol deviations affecting the PK variables will be defined in the protocol deviation document. The process to review major protocol deviations potential impact on PK parameters will be ongoing and the final Sparse PK Sampling Analysis Set will be determined during data review meeting.

Where possible, PK profile will be assessed following PK modeling, for each subject within the Sparse PK Sampling Analysis Set. This analysis will be described in a separate data analysis plan and reported in a standalone report.

5.8 PD Analysis Set

The PD Analysis Set includes all subjects in full PK/PD subgroup who have a sufficient number of PD measurements.

5.9 PK/PD Relationships Set

The PK/PD Relationships Set includes all subjects who receive at least one dose of IMP, have at least one valid plasma triptorelin concentration and have at least one PD measurement (PD markers: E_2, FSH and LH).

The PK/PD Relationships Set will be used to describe, where possible, the relationships between plasma triptorelin concentration and PD markers (E_2, FSH and LH) according to the actual treatment received for each subject. This analysis will be described in a separate data analysis plan and reported in a standalone report.

6 DATA HANDLING

6.1 Time points and Visit Windows

Day 1 is defined as the day of first dose of IMP treatment. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1.

Unless specified otherwise, baseline is defined as the last available assessment prior to the first dose of IMP; if assessment time and/or drug taken time is not collected, the assessment performed on the same day as first dose of IMP will be considered as baseline; if assessment date is missing, the assessments at the scheduled visits of screening (Visit 1) and Day 1 or baseline (Visit 2) will be considered as pre-baseline visits in flag baseline.

By-visit analyses on data will be analysed according to the scheduled visits outlined in the protocol and/or eCRF (Week xx). No visit windows will be applied for summary and analysis.

If subject early discontinued study, the measured safety and efficacy variables at early discontinued visit are collected in "End of study/early withdrawal visit". Then the early withdrawal visit of safety and efficacy endpoints (except PD sampling) will be re-mapped to the visits using the time windows in Table 1.

Table 1 Scheduled Visits and Time Window

Scheduled Visit at Study Site	Target Day of the Visit	Protocol Visit Window	Time Window to Re-map End of Study Visit or Early Withdrawal Visit
Baseline	Day 1	Day 1	Day 1
Week 4	Day 29	Target Day ± 3 days	Day 26 – Day 53
Week 8	Day 57	Target Day ± 3 days	Day 54 – Day 81
Week 12	Day 85	Target Day ± 3 days	Day 82 – Day 109
Week 16	Day 113	Target Day ± 3 days	Day 110 – Day 137
Week 20	Day 141	Target Day ± 3 days	Day 138 – Day 165
Week 24	Day 169	Target Day ± 3 days	Day 166 – Day 193
Week 28	Day 197	Target Day ± 3 days	Day 194 – Day 221
Week 32	Day 225	Target Day ± 3 days	Day 222 – Day 249
Week 36	Day 253	Target Day ± 3 days	Day 250 – Day 277
End of study visit (Week 40)	Day 281 or within 15 days after menses recovery	Target Day ± 3 days	≥ Day 278

Data from end of study visit or early termination assessments will be combined with data from scheduled visits in the by-visit analyses only if no scheduled visit data for the same parameters at that visit.

The "final visit" will be added after all scheduled visits in by-visit analyses on safety data including lab tests, ECG, vital signs, physical/pelvic examination and pelvic type B ultrasound scan. The final visit means the last available measurements at scheduled or unscheduled visits after first study dose during the study.

6.2 Handling of Dropouts or Missing Data

No data imputation will be performed for missing efficacy and safety variables, except efficacy endpoints of percentage of subjects castrated. If E_2 measurement is missing, the last available E_2 measurement at post-baseline visits will be used in deriving subjects castrated.

For laboratory values or concentration data below the lower limit of quantification (LLOQ) like "<xxx" or "<=xxx", or above the upper limit of quantification (ULOQ) like ">xxx" or ">=xxx", LLOQ or ULOQ

(xxx) will be used for calculation of descriptive statistics. The original laboratory values or concentration data ("<xxx", "<=xxx", ">xxx" or ">=xxx") are presented in the listing.

6.2.1 Handling of triptorelin BLQ concentration values

For the full PK/PD subgroup (with full PK sampling schedule) only, and for descriptive statistics only (not for the individual listings):

- For the first administration of study drug, BLQ data must be substituted by 0 for concentrations measured before the first quantifiable concentration, and by missing after the first quantifiable concentration.

- For any other administration all BLQ must be set as missing in the dataset

For the sparse PK groups all BLQ must be set as missing in the descriptive statistics datasets.

For further details of the descriptive statistics for triptorelin concentration data please refer to section 7.8.

6.2.2 Partial dates

If the date of endometriosis diagnosis or date of endometriosis surgery is a partial date, the first day of known year and/or month will be used to calculate duration.

For AEs, concomitant medications, and concurrent procedures, the following conventions will be used for imputing partial dates:

- If day (and month) is missing for AE onset date, or start date of a concomitant medication, or date of concurrent procedure, the partial date will be set to
  - date of first dose of IMP, if the known year (and month) is same as the year (and month) of first dose of IMP and no other information indicating the date is before first dose of IMP;
  - the first day of the known year (and month), if the year (and month) of the partial date is different from the year (and month) of the first dose of IMP or other information indicating the date is before first dose of IMP;
- If day (and month) is missing for AE stop date, or the stop date of a concomitant medication, this day will be set to the last day of the known year (and month) that AE or medication occurred;
- If AE onset date, or start date of a concomitant medication, or date of concurrent procedure is completely missing, this date will be set to date of the dose of IMP;
- If the imputed start date is after stop date, the start date will be set to the stop date.

Partial dates will be presented as original in all listings, and imputed dates will not be presented in listings.

6.3 Pooled Center

If cities have number of PP subjects less than average number of subjects per centre (total number of PP subjects divided by total number of centres), these cities will be pooled together or pooled to other cities to keep all cities with number of subjects equal to or more than average number of subjects per centre.

7 STATISTICAL METHODS

7.1 General Principles

The statistical analyses will be performed in accordance with ICH E9 guideline [1, 3, 4].

Statistical analysis of the efficacy and safety data will be performed by Covance, managed by the Sponsor's Biometry Department.

All data processing, summarisation and analyses will be performed using Version 9.3 (or higher) of the Statistical Analysis System (SAS®) statistical software package.

Unless specified otherwise, data will be displayed using the following treatment group labels, in the order presented:

Triptorelin Pamoate PR 3-month

Triptorelin Acetate PR 1-month

Total (if total is presented for all treatment groups)

Continuous variables will be summarised by the number of subjects (n), mean, standard deviation (SD), median, minimum and maximum. The summary statistics will be displayed for visits where there are non-missing data for at least two subjects in one or more treatment groups. Mean, median and SD will have 1 extra decimal place than the actual values. If 95% CI of mean is presented, lower and upper confidence interval values should be presented to one decimal place more than the raw/derived data (i.e. to the same number of decimal places as the mean). Minimum and maximum values will be reported with the same decimal places as the actual values. A maximum 3 decimal places will be displayed for all summary statistics.

For categorical variables, summaries will include counts of subjects or events and percentages (1 decimal), 0% will not be presented. Percentages will be calculated using a denominator of all subjects in a specified population unless otherwise specified. The denominator will be specified in a footnote to the tables for clarification if necessary. Percentages in the summary tables will be rounded and thus may not always add up to exactly 100 percent. The 95% CI of rate or rate difference will have 2 decimal places.

In the summary tables, p-values will be rounded to 4 decimal places if appropriate. If a p-value is greater than 0.9999, then ">0.9999" will be presented; if a p-value is less than 0.0001, then "<0.0001" will be presented.

All data collected during the study will be presented in listings by treatment group, study centre, subject identifier, and visit (where applicable), unless otherwise specified.

All text fields must be left justified and numeric or numeric with some text specification (e.g.: not done, unknown, <4.5 …) must be decimal justified. Dates will be presented in the format [ddMMMyyyy] and times in the format [hh:mm] in a 24-hour basis.

7.2 Subject Disposition and Data Sets Analysed

Subject disposition will be listed and summarised by treatment group and overall and the following subjects will be presented:

- Number of subjects screened (overall);
- Number of screen failures and reason for non-randomised subjects (overall)

- Number of subjects randomised;
- Number of subjects randomised and not treated;
- Number of subjects treated;
- Number of subjects who completed Week12, Week 24 and study;
- Number of subjects discontinued study, and reason for discontinuation;
- Number of subjects included in each analysis set (Randomised, Safety, FAS, PP, Full PK Profile, Sparse PK Sampling, PD, PK/PD Relationships).

A summary of subject enrollment by centre will also be provided by treatment group and overall for the randomised subjects.

A summary of subjects completed scheduled visits will be presented by treatment group and overall for the randomised subjects.

7.3 Protocol Deviations

Major protocol deviations affecting primary efficacy endpoint leading to exclusion from the PP set will be summarised by treatment group and overall for the randomised subjects.

Major protocol deviations affecting PK variables leading to exclusion from the Full PK Profile Analysis Set and/or Sparse PK Sampling Analysis Set will also be summarised by treatment group and overall for the safety set.

All protocol deviations will be listed for the randomised subject with flags indicating if deviations are major or minor PDs.

A separate listing for major protocol deviations will be displayed. Flags indicating deviations affecting efficacy endpoints and/or PK/PD variables will also be included in the listing.

7.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarised by treatment group and overall for these analysis sets: randomised, safety (if different from randomised), PP and FAS, including the below variables:

- Age (years) is reported from CRF;
- Race, Ethnicity;
- Weight (kg), height (cm), body mass index (kg/m^2) (BMI) [calculated as ($weight/height^2$) where weight is in kg and height is in m];
- Gynaecological history:
  - Duration of endometriosis diagnosis (months) [calculated as (informed consent date – date of endometriosis diagnosis +1)/ 30.4375 and rounded to 1 decimal place];
  - Method of diagnosis
  - If having endometriosis surgery before; duration of endometriosis surgery (months) [calculated as (informed consent date – date of endometriosis surgery +1)/ 30.4375 and rounded to 1 decimal place];

- Age at menarche, number of pregnancies, number of births
- If having regular menses during the last six months
- Number of days for shortest cycle and Number of days for longest cycle

Standard descriptive statistics will be presented for the continuous variables and the total counts and percentages of subjects will be presented for the categorical variables. No formal tests of statistical significance will be performed on the demographic and baseline data.

Other baseline measurements (such as E_2, FSH and LH concentrations, VAS, lab test, vital signs, ECG, physical/pelvic examination, pelvic type B ultrasound scan) will be summarised by treatment group with the post-baseline measurements.

7.4.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version number is the newest version used in Covance coding system at the time of analysis). All medical history will be listed and summarised by the number and percentage of subjects with any medical history for randomised set by system organ class (SOC) and preferred term (PT) for each treatment group and overall.

7.4.2 Previous and Concomitant Medications

Prior medications for endometriosis and other medications received prior to or concomitantly with study treatment will be coded using the WHO Drug Dictionary (version number is the newest version used in Covance coding system at the time of analysis), Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications for endometriosis from eCRF will be summarised separately by the number and percentage of subjects with any medications for randomised set by anatomical level (ATC Level 1), therapeutic level (ATC Level 2) and generic term for each treatment group and overall.

Prior medications are those taken prior to first study dose of IMP. Concomitant medications are those taken on or after the first dose of IMP.

Prior medications and concomitant medications will be summarised separately by the number and percentage of subjects with any medications for randomised set by anatomical level (ATC Level 1), therapeutic level (ATC Level 2) and generic term for each treatment group and overall.

The number and percentage of subjects taking add-back treatment during the study will be summarised separately by anatomical level (ATC Level 1), therapeutic level (ATC Level 2) and generic term for each treatment group and overall.

Prior medications for endometriosis will be separately listed. Prior and concomitant medications will be presented in the same listing with flags indicating prior or concomitant.

7.4.3 Previous and Concomitant Non-drug Therapies

Prior and concomitant non-drug therapies will be coded using MedDRA (version number is the newest version used in Covance coding system at the time of analysis). All prior and concomitant non-drug therapies will be listed and summarised by the number and percentage of subjects with any non-drug therapies for randomised set by system organ class (SOC) and preferred term (PT) for each treatment group and overall.

Prior non-drug therapies are those taken prior to first study dose of IMP. Concomitant non-drug therapies are those taken on or after the first dose of IMP.

Prior non-drug therapies and concomitant non-drug therapies will be summarised separately by the number and percentage of subjects with any therapies for randomised set by therapy reason for each treatment group and overall.

Prior and concomitant non-drug therapies will be presented in the same listing with flags indicating prior or non-drug therapies.

7.4.4 Concomitant Surgical Procedures

Concomitant surgical procedures will be coded using the MedDRA (version number is the newest version used in Covance coding system at the time of analysis). All concomitant surgical procedures will be listed and summarised on the number and percentage of subjects with any surgical procedures for randomised set by surgical reason, SOC and PT for each treatment group and overall.

Concomitant surgical procedures will be presented in the listing.

7.5 Study Drug Administration

Study drug administration will be summarised separately through Week 12 and Week 24 by treatment group and overall for safety subjects, including the below variables:

- Number of injections during Week 12, Week 24
- Total actual dose during Week 12, Week 24
- Treatment compliance through Week 12, Week 24 and compliance groups (grouped as <80%, 80-120%, >120%)

Standard descriptive statistics will be presented for the continuous variables and the total counts and percentages of subjects will be presented for the categorical variables. No formal tests of statistical significance will be performed on the study drug administration.

Treatment compliance will be calculated as follows:

- Treatment compliance through Week 12 in triptorelin pamoate PR 3-month group = 100% * actual dose administered before Week 12 / (total planned dose administered before Week 12);
- Treatment compliance through Week 24 in triptorelin pamoate PR 3-month group = 100% * sum of actual dose administered through Week 24 / (total planned dose administered through Week 24);
- Treatment compliance through Week 12 in triptorelin acetate PR 1-month group = 100% * sum of actual dose administered before Week 12 / (total planned dose administered before Week 12).
- Treatment compliance through Week 24 in triptorelin acetate PR 1-month group = 100% * sum of actual dose administered through Week 24 / (total planned dose administered through Week 24).

7.6 Efficacy

7.6.1 Primary Efficacy Analysis

The primary efficacy analysis is to compare the percentage of subjects castrated ($E_2 \leq 184$ pmol/L or 50 pg/mL) at Week 12 in triptorelin pamoate PR 3-month and triptorelin acetate PR 1-month groups on the PP subjects using as-treated assignments.

The null hypothesis for the primary efficacy analysis is that triptorelin pamoate PR 3-month is inferior to triptorelin acetate PR 1-month. The alternative hypothesis is that triptorelin pamoate PR 3-month is noninferior to triptorelin acetate PR 1-month, where the pre-specified non-inferiority margin is -10%:

$$H_0: P_{3\text{-month}} - P_{1\text{-month}} \leq -10\%$$

$$H_a: P_{3\text{-month}} - P_{1\text{-month}} > -10\%$$

Where $P_{3\text{-month}}$ denotes the percentage of subjects ($E_2 \leq 184$ pmol/L or 50 pg/mL) for triptorelin pamoate PR 3-month at Week 12, $P_{1\text{-month}}$ denotes the percentage of subjects ($E_2 \leq 184$ pmol/L or 50 pg/mL) for triptorelin acetate PR 1-month at Week 12.

The number and percentage of subjects castrated (E2≤184 pmol/L or 50 pg/mL), and its 95% asymptotic CI will be summarised for each treatment group at Week 12. The difference in percentage of subjects castrated (triptorelin pamoate PR 3-month – triptorelin acetate PR 1-month) and the 2-sided 95% CI of the difference will also be presented and calculated using the Miettinen and Nurminen method, stratified by randomisation stratification factors (endometriotic surgical history and the severity of endometriosis-associated pelvic pain at baseline) with sample size weighting [5]. In a case where the stratification factor recorded in the eCRF and IWRS are inconsistent, the eCRF data will be retained included as the randomization stratification factors as the covariates. If the lower limit of the 95% CI for the difference is >-10%, triptorelin pamoate PR 3-month non-inferiority to triptorelin acetate PR 1-month will be confirmed.

The sensitivity analysis will be performed on the same analyses adding centre in the above Miettinen and Nurminen method.

The difference in percentage and its 2-sided 95% CI are also calculated using the Miettinen and Nurminen method without stratification factors for support analyses.

The primary efficacy analyses will be repeated for the FAS subjects using as-randomised assignments.

7.6.2 Secondary Efficacy Analysis

The analyses of secondary efficacy endpoints (see Section 3.2) will be performed in the PP subjects and the FAS subjects using as-randomised assignments.

Percentage of Subjects Castrated (E2≤184 pmol/L or 50 pg/mL) at Weeks 4 and 8 and Percentage of Subjects Castrated (E2≤110 pmol/L or 30 pg/mL) at Weeks 4, 8 and 12:

The number and percentage of subjects castrated (according to each criterion) will be presented by treatment group for each visit. The difference in percentage between the treatment groups and its 2-sided 95% CI will be presented and calculated using the same method as primary efficacy analysis.

Change in Endometriosis-associated Pelvic Pain (by 10 cm VAS) at Weeks 4, 8 and 12:

Endometriosis-associated pelvic pain measured by 10 cm VAS and change from baseline, will be summarised by treatment groups at each time point, using summary statistics (n, mean, median, SD and minimum and maximum values) and the 95% CI for the true difference in mean VAS score and VAS change from baseline scores will be presented.

The 95% CI for the difference in mean and change from baseline VAS score are calculated using a linear model for repeated measurements adjusting for treatment group and its interaction with visit, and randomisation stratification factors (endometriotic surgical history and the severity of endometriosis-associated pelvic pain at baseline) and its interaction with treatment group CCI In a case where the stratification factor recorded in the eCRF and IWRS are inconsistent, the eCRF data will be retained. This will be applied to all analyses that include the randomization stratification factors as the covariates. The SAS code for this model to be used is shown below:

```
CCI
                                                                    ;
```

In case of model convergence issues, this will be reported in the study report and additional covariance structures will be investigated with the following order: heterogeneous compound symmetry (type=csh), heterogeneous toeplitz (type=toeph), heterogeneous autoregressive (1) (type=arh(1)), and variance components (type=vc).

Serum E_2, FSH and LH Concentrations at Weeks 4, 8 and 12:

Serum E_2, FSH and LH concentrations and change from baseline will be summarised at each time point, using descriptive statistics (n, mean, median, SD and minimum and maximum values) and the 95% CI for the difference between treatment groups in mean concentration values and mean change from baseline values will be presented for each parameter.

The 95% CI for the difference in mean and change from baseline values are calculated using a linear model for repeated measurements adjusting for baseline value and its interaction with visit, treatment group and its interaction with visit, and randomisation stratification factors (endometriotic surgical history and the severity of endometriosis-associated pelvic pain at baseline) and its interaction with treatment group. In a case where the stratification factor recorded in the eCRF and IWRS are inconsistent, the eCRF data will be retained. Baseline and its interaction with visit will be added in the above SAS code.

Time to Menses Recovery:

Time to menses recovery will be defined as the time (in days) between date of last dose of study drug and date of first day the subject observed menstrual bleeding of the next menstrual period. Any subjects withdrawing from the study without menstrual bleeding will be censored in the analysis at the date of withdrawal, and any subjects without menstrual bleeding prior to the end of study visit will be censored in this analysis at the date of the last known menses status study visit. Any subjects who doesn't stop menses during the treatment duration (V2 till V8) are excluded this analysis. "Stop menses" is considered as at least one answer "No" for the question "Is the menses recovered since last visit" in CRF page "Status of Menses" at least 2 consecutive menses stop during treatment duration (V2 till V8).

The number and percentage of subjects with menses recovery and censored subjects and their censor reasons will be summarised. The median time, 25th and 75th quartile times and their 95% CIs will be estimated using the Kaplan-Meier method; Kaplan-Meier curves will be plotted.

7.6.3 Subgroup Analysis

The primary efficacy endpoints and secondary efficacy endpoints (except time to menses recovery) will be analysed by subgroups of randomisation stratification factors:

- Endometriotic surgical history (previous surgery, no previous surgery)
- Severity of endometriosis-associated pelvic pain at baseline (VAS>3 cm, VAS≤3cm).

7.6.4 Exploratory Analysis

The analyses of exploratory efficacy endpoints (see Section 3.3) will be performed on the FAS subjects using as-randomised assignments.

Percentage of subjects castrated 1) E_2≤184 pmol/L (50 pg/mL) 2) E_2≤110 pmol/L (30 pg/mL)) at Week 24:

The number and percentage of subjects castrated (according to each criterion) will be presented by treatment group at Week 24. The difference in percentage between the treatment groups and its 2-sided 95% CI will be presented and calculated using the same method as primary efficacy analysis.

Change in endometriosis-associated pelvic pain (by 10cm VAS) at Weeks 16, 20 and 24 and the end of study visit compared to baseline:

Endometriosis-associated pelvic pain measured by 10 cm VAS and change from baseline, will be summarised by treatment groups and overall at each time point, using summary statistics (n, mean, median, SD and minimum and maximum values) and the 95% CI for the true difference in mean VAS score and VAS change from baseline scores will be presented.

The 95% CI for difference in mean and change from baseline values are calculated using MMRM, same as those used in secondary analyses of VAS.

The mean and change from baseline of VAS at each time point are also analysed by subgroups of baseline VAS (VAS>3 cm, VAS≤3cm).

Serum E2, FSH and LH Concentrations at Week 24:

Serum E2, FSH and LH concentrations and change from baseline will be summarised at Week 24, using descriptive statistics (n, mean, median, SD and minimum and maximum values) and the 95% CI for the difference between treatment groups in mean concentration values and mean change from baseline values will be presented for each parameter.

The 95% CI for the difference in mean and change from baseline values are calculated using MMRM, same as those used in secondary analyses of VAS.

The PK/PD relationship will be explored (PD markers being E2, FSH and LH).

The data for subject individual plasma triptorelin concentration and PD markers in the each treatment groups will be combined to explore the relationships between PK concentrations and PD markers on the PK/PD relationships analysis set. PK/PD modelling will be described in a separate data analysis plan and reported in a standalone report.

7.7 Safety

All safety data will be included in the data listings. Analyses and summary tables will be based on the Safety Set. Safety endpoints will be analysed using descriptive statistics.

7.7.1 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as any AE that occurs or worsens on or after the first dose of IMP, through 112 days (16 weeks) after last injection for triptorelin pamoate PR 3-month groups or through 56 days (8 weeks) after injection for triptorelin acetate PR 1-month group. Non-TEAEs and TEAEs will be separately summarised in tables and all AEs will be presented in the listing with flag of TEAE status.

All adverse events (AEs) recorded on the eCRF will be coded to SOC and PT using the MedDRA dictionary (version number is the newest version used in Covance coding system at the time of analysis). A subject will be counted at most once within a SOC and PT in summary tables.

In the summary table of TEAEs, the numbers and percentages of subjects and events will be tabulated and presented by treatment groups and overall for the following categories:

- Any TEAEs
- TEAEs with maximum intensity (Severe, Moderate, Mild)
- Serious TEAEs
- Drug-related TEAEs
- Drug-related serious TEAEs
- TEAEs leading to drug withdrawal
- TEAEs leading to drug interruption
- Serious TEAEs leading to drug withdrawal
- Serious TEAEs leading to drug interruption
- TEAEs leading to death

The numbers and percentages of subjects and events will be also be separately summarised by SOC and PT (sorted alphabetically) for each treatment group and overall as the above AE categories. The TEAEs with intensity of Severe will be separately summarised by SOC and PT (sorted alphabetically) for each treatment group and overall. The TEAEs and drug-related TEAEs will be also separately summarised by maximum intensity, SOC and PT (sorted alphabetically) for each treatment group and overall.

TEAEs or drug-related TEAEs with PTs observed ≥5% or ≥10% of subjects in any one of the treatment groups will be separately summarised by SOC and PTs.

In the event of multiple events being reported by the same subject, the maximum intensity (severe, missing, moderate, mild) and the most serious causality (related, not related) will be chosen. If severity is missing for one event and the subject had no intensity of severe in the same category events, “missing” row should be added after severe in the summary tables with maximum intensity.

The following AEs for each subject will be separately listed, including SOC, PT, and the original (verbatim) term reported by Investigator:

- All AEs
- Serious AEs
- Drug-related AEs
- AEs leading to drug withdrawal
- Deaths

7.7.2 Laboratory Evaluations

The central laboratory test results will be collected at screening (Visit 1), Week 12 (Visit 5) and Week 24 (Visit 8), including the following parameters:

- Haematology: red blood cell (RBC) count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) and platelet count;
- Biochemistry: urea, creatinine, total bilirubin, conjugated bilirubin, chloride, bicarbonate, sodium, potassium, calcium, inorganic phosphate, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, albumin, total protein, total cholesterol, triglycerides, fasting glucose;
- Urinalysis: pH, protein, ketones, glucose, bilirubin, blood, urobilinogen and specific gravity;

Standard international units will be used for summarising quantitative laboratory parameters. Out of reference range values will be flagged as high (H) or low (L) in the listings.

The quantitative laboratory data will be summarised using standard descriptive statistics on actual values and change from baseline at each scheduled visit and final visit for the Safety subjects.

Shift tables presenting movement in and out of reference range (low, normal, high) from baseline to each scheduled post-baseline visit and final visit will be presented by each treatment group and overall. Shift tables presenting movement of clinical evaluation (normal, abnormal not clinically significant, abnormal clinically significant) from baseline to each scheduled post-baseline visit and final visit will be presented by each treatment group and overall as well.

Subjects who became pregnant during the study will be summarised by treatment groups.

Potentially Clinically Significant Abnormalities (PCSA) for Laboratory Tests

The PCSA criteria of some selected laboratory tests in this study are listed in the below table. The number and percentage of subjects with PCSA for each below parameter will be summarised by treatment group and overall at each scheduled visit, final visit and any post-baseline visit. The number and percentage of subjects with abnormal PCSA values (PCSA-low and PCSA-high) at any post-baseline will be summarised by different baseline values (normal, abnormal) and parameters.

Table 2 PCSA Criteria for Laboratory Tests

Lab Parameter	PCSA – Low Criteria	PCSA– High Criteria	Unit
HGB	≤ 80		g/L
RBC	< 2.8		TI/L
HCT	< 0.32 and 0.03 decrease from baseline		%
WBC	≤ 2.0	≥ 29	GI/L
Neutrophil	< 1	> 13	GI/L
Lymphocyte	< 0.3	> 11.0	GI/L
Monocytes		> 2.3	GI/L
Eosinophil		> 1	GI/L
Basophils		> 0.8	GI/L
Platelets	< 50	≥ 700	GI/L
Total Bili		> 3 x ULN	µmol/L
Dir Bili		> 3 x ULN	µmol/L
Alkaline Phosphatase		≥ 3 x ULN	U/L
ALT(SGPT)		≥ 3 x ULN	U/L
AST(SGOT)		≥ 3 x ULN	U/L
GGT		≥ 3 x ULN	U/L
Urea Nitrogen		> 10	mmol/L
Glucose, Fasting	< 3.9	≥ 7.1	mmol/L
Triglycerides		>1.4 (18-20 years) >1.63 (21-30 years) > 1.99 (31-40 years) >2.42 (41-50 years)	mmol/L mmol/l mmol/l mmol/l
Cholesterol		>5.48 (18-20 years) >5.64 (21-30 years) > 6.21 (31-40 years) ->6.85 (41-50 years)	mmol/L mmol/l mmol/l mmol/l
Creatinine		> 154	µmol/L
Calcium	< 1.75	> 3.12	mmol/L
Phosphorus	< 0.65	>1.8	mmol/L
Total Protein	< 40		g/L
Alb BCG	< 25		g/L
Sodium	< 125	> 147	mmol/L
Potassium	< 3.0	> 6	mmol/L
Chloride	≤ 90	≥ 115	mmol/L

All laboratory data collected during the study will be presented in subject listing with flags indicating out of reference range (low, high), clinical evaluation (abnormal not clinically significant, abnormal clinically significant). If a subject has at least one lab measurement meeting PCSA criteria, all data of that lab parameter will be presented in a separate listing with flag indicating PCSA-low or PCSA high.

7.7.3 Electrocardiograms

The 12-lead ECG will be measured at screening (Visit 1), Week 12 (Visit 5) and Week 24 (Visit 8) including heart rate (beats/min), PR interval (msec), QRS interval (msec), QT interval (msec), QTc interval (msec) and investigator interpretation of ECG. Fridericia corrected QT (QTcF) interval (msec) will be calculated as $(QT/(60/HR)^{1/3})$.

The quantitative ECG data will be summarised using standard descriptive statistics on actual values and change from baseline at each scheduled visit and final visit for the Safety subjects.

Shift tables of investigator assessment of ECG (normal, abnormal not clinically significant, abnormal clinically significant) from baseline to each scheduled post-baseline visit and final visit will be presented by treatment group and overall.

Potentially Clinically Significant Abnormalities (PCSA) for ECG

Any case with none sinus rhythm is considered to be PCSA. The PCSA criteria in subjects with sinus rhythm are listed in the table below. The number and percentage of subjects with PCSA for each below parameter will be summarised by treatment group and overall at each scheduled visit, final visit and any post-baseline visit. The number and percentage of subjects with abnormal PCSA values (PCSA-low and PCSA-high) at any post-baseline will be summarised by different baseline values (normal, abnormal) and parameters

Table 3 PCSA Criteria for ECG

ECG test Name	PCSA – Sinus Rhythm (Y/N)*	PCSA – Low Criteria	PCSA – High Criteria	PCSA – Chang from baseline	Normal range	Unit
Heart Rate (collected from CRF)	Y	< 50	≥ 120	NA	60-100	bpm
PR Interval (collected from CRF)	Y	< 120	≥ 240	NA	120-200	ms
QRS Interval (collected from CRF)	Y	NA	≥ 120	NA	60-100	ms
QT interval (collected from CRF)	Y	NA	NA	NA	320-440	ms
QT Interval, Corrected (collected from CRF)	Y	≤300	≥ 470	≥ + 45	>300 and <440	ms
QTcF (calculated by programming)	Y	≤300	≥ 470	≥ + 45	>300 and <440	ms

*Y/N= yes/no; Y = sinus rhythm.

All ECG data collected during the study will be presented in subject listings. If a subject has at least one ECG measurement meeting PCSA criteria, all her data for that ECG parameter will be presented in a separate listing with flag indicating PCSA-low or PCSA high.

7.7.4 Vital Signs

The vital signs will be measured at each visit during treatment and the end of study visit, including systolic blood pressure (mmHg), diastolic blood pressure (mmHg) and heart rate (beats/min).

Descriptive statistics on actual values and change from baseline will be summarised by treatment group and overall at each scheduled visit and the final visit for the Safety subjects.

Potentially Clinically Significant Abnormalities (PCSA) for Vital Signs

The PCSA criteria for selected vital signs in this study are listed in the table below. The number and percentage of subjects with PCSA for each below parameter will be summarised by treatment group and overall at each scheduled visit, final visit and any post-baseline visit. The number and percentage of subjects with abnormal PCSA values (PCSA-low and PCSA-high) at any post-baseline will be summarised by different baseline values (normal, abnormal) and parameters.

Table 4 PCSA Criteria for Vital signs

Parameter	PCSA – Low Criteria	PCSA – High Criteria	Unit
Heart rate	≤50	≥120	bpm
Systolic blood pressure	≤80	≥160	mmHg
Diastolic blood pressure	≤50	≥100	mmHg

The normal ranges for vital signs are defined as below:

- Heart rate: 60-100 bpm
- Systolic blood pressure: 90-139 mmHg
- Diastolic blood pressure: 60-89mmHg

Note: the number is inclusive.

All vital signs data collected during the study will be presented in subject listings. If a subject has at least one vital sign measurement meeting PCSA criteria, all her data for that vital sign parameter will be presented in a separate listing with flag indicating PCSA-low or PCSA high.

7.7.5 Physical/Pelvic Examination

The physical/pelvic examination will be performed at screening (Visit 1), Week 12 (Visit 5) and Week 24 (Visit 8).

Shift tables of test results (normal, abnormal not clinically significant, abnormal clinically significant) from baseline to each scheduled post-baseline visit and final visit will be presented by treatment group and overall.

All physical/pelvic examination data collected during the study will be presented in subject listings.

7.7.6 Pelvic type B ultrasound

The pelvic type B ultrasound scan will be performed at screening (Visit 1), Week 12 (Visit 5, optional based on investigator judgment) and Week 24 (Visit 8).

Shift tables of test results (normal, abnormal not clinically significant, abnormal clinically significant) from baseline to each scheduled post-baseline visit and final visit will be presented by each treatment group and overall.

All pelvic type B ultrasound scan data collected during the study will be presented in subject listings.

7.7.7 Hormones

Serum E2, FSH and LH concentrations at Week 40 will be listed separately for those subjects with menses not recovered before Week 40.

7.8 Pharmacokinetics

The individual plasma triptorelin concentration is measured in all subjects receiving study drug at Day 1 (Visit 2), Week 4 (Visit3), Week 8 (Visit 4), Week 12 (Visit 5) and Week 24 (Visit 8). Additional sampling is performed for subjects within the PK/PD subgroup.

- The individual plasma triptorelin concentration will be summarised using descriptive statistics (n, mean, SD, %CV, geometric mean, geometric CV, median, minimum and maximum) by treatment group at each scheduled visit for the Sparse PK Sampling set.
- The individual plasma triptorelin concentrations for the Full PK Profile Analysis set will be summarised using descriptive statistics (n, mean, SD, %CV, geometric mean, geometric CV, median, minimum and maximum) by time-point (described as hours/days post-dose), for each treatment group, following each administration.
- To compute descriptive statistics, all BLQ values must be replaced by missing/zero in the data set according to the rules set in section 6.2.1. BLQ values substituted by 0 are included in the calculation of descriptive statistics whereas missing values are ignored. The descriptive statistics should be displayed by visit/time point, and by treatment group only if at least 2/3 (2 out of every 3 values) of the data are available and above the limit of quantification. Otherwise, only minimum and maximum are reported. Individual and mean plasma concentration time profiles, as well as spaghetti plots, on the Full PK Profile Analysis Set will be generated separately based on a dedicated PK analysis plan.

7.9 Interim Analysis

No interim analyses will be performed.

8 CHANGES IN PLANNED ANALYSES

Not applicable.

9 REFERENCES

1 ICH. *Statistical Principles for Clinical Trials*, Guideline E9, 1998. Available at http://www.emea.eu.int/pdfs/human/ich/036396en.pdf

2 ICH. *ICH E3 Guideline: Structure and Content of Clinical Study Reports Questions & Answers*, 2012. Available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf

3 Phillips A and Haudiquet V. *ICH E9 guideline "Statistical principles for clinical trials": a case study*. Statistics in Medicine 2003; 22:1-11

4 Brown D J. *ICH E9 guideline "Statistical principles for clinical trials": a case study. Response to A. Phillips and V. Haudiquet.* Statistics in Medicine 2003; 22:13-17

5 Miettinen O and Nurminen M. *Comparative Analysis of Two Rates.* Statistics in Medicine, VOL.4, 213-226 91985)

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10 APPENDICES

Appendix I - Schedule of Events

Table 5 Study Procedures and Assessments (All Subjects)

	Screening period	Treatment period							Follow up period [a]			
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	End of study/early withdrawal visit
Procedures and assessments	**Screening up to -5 weeks**	**Baseline (1st to 5th day of menses)**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**within 15 days after menses recovery or Week 40[b]**
Visit window (days)	**-35 to -1**	**Day 1**	**Day 29 ±3**	**Day 57 ±3**	**Day 85 ±3**	**Day 113 ±3**	**Day 141 ±3**	**Day 169 ±3**	**Day 197 ±3**	**Day 225 ±3**	**Day 253 ±3**	**Day 281 ±3**
Informed consent	X											
Demography	X											
Significant medical or surgical history	X											
Prior medications for endometriosis	X											
Inclusion and exclusion criteria	X	X										
E2, FSH and LH		X[c]	X[c]	X[c]	X[c]			X				X[d]
VAS		X	X	X	X	X	X	X				X
Physical examination[e]	X				X			X				
Pelvic examination	X				X			X				
Vital signs	X	X	X	X	X	X	X	X				X

Blood Biochemistry[f]	X				X			X				
Haematology[f]	X				X			X				
Urinalysis[f]	X				X			X				
Urine pregnancy test	X	X										
12-lead ECG	X				X			X				
Pelvic type B ultrasound scan	X[g]				X[h]			X				
Sparse PK assessments		X[c]	X[c]	X[c]	X[c]			X				
Randomization		X										
Study drug injection (3-month formulation)		X[i]			X							
Study drug injection (1-month formulation)		X[i]	X	X	X	X	X					
AEs	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medication/therapies	X	X	X	X	X[j]	X[j]	X[j]	X	X	X	X	X
Status of menses	X	X	X	X	X	X	X	X	X	X	X	X

AE=adverse event; E_2=oestradiol; ECG=electrocardiogram; FSH=follicle stimulation hormone; LH=luteinising hormone; PK=pharmacokinetic; VAS=visual analogue scale

a during the follow up period, the first visit after menses recovery, or Week 40 (whichever is earlier) will be considered the final visit (end of study). The end of study visit should be a clinic visit. Follow up visits prior to the end of study visit will be telephone contact visits

b or upon early withdrawal from the study

c samples taken predose, where applicable

d only if subject's menses do not recover before Week 40

e subject height and weight will be assessed at screening only

f samples for clinical laboratory testing will be taken after at least 8 hours fasting

g a result within 1 month prior to the screening visit will be acceptable

h optional, based on the subject's disease condition, as judged by the investigator

i study treatment must be initiated during the subject's follicular phase (first to fifth day of menses period)

j from Week 12, after the primary endpoint evaluation, "add back" treatment will be permitted if needed according to the investigator's judgment. "Add back" treatment will be recommended as, but not limited to, tibolone 2.5 mg once daily

Table 6 Full PK/PD Assessments day 1 to Week 12 (PK/PD Subgroup Subjects)

Assessment[a]	Treatment period										
	Day 1	Week 1 (hours post Day 1 dosing)			Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12
Assessment time (study day/hours postdose)[b]	**Day 1**	**24**	**48**	**168**	**Day 15**	**Day 22**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**
PK (3M)	X[c]	X	X	X	X	X	X	X	X		X[c]
PK (1M)	X[c]	X	X	X	X	X	X[d]		X[d]	X	X[d]
PD (E2, FSH and LH)				X	X	X					
AEs	X	X			X	X	X	X	X	X	X
Prior and concomitant medication/therapies	X	X			X	X	X	X	X	X	X

1M=triptorelin acetate PR 1-month; 3M=triptorelin pamoate PR 3-month; AE=adverse event; E2=oestradiol; FSH=follicle stimulating hormone; LH=luteinising hormone; PD=pharmacodynamics; PK=pharmacokinetics.

a assessments to be conducted with samples from the subjects in the full PK/PD subgroup (comprising up to 16 subjects receiving 3M and up to 16 subjects receiving 1M; to be enrolled at selected sites) only

b time windows for full PK/PD assessments will be defined in the Study Manual

c samples taken predose and 0.5, 1, 2, 4, 8 and 12 hours postdose

d samples taken predose

Table 7 Full PK/PD Assessments Week 13 to End of Study (PK/PD Subgroup Subjects)

Assessment[a]	Treatment period												
	Week 12 (hours post Week 12 dosing)			Week 14	Week 15	Week 16	Week 18	Week 20	Week 24	Week 28	Week 32	Week 36	End of study/ early withdrawal
Assessment time (study day/hours postdose)[b]	**24**	**48**	**168**	**Day 99**	**Day 106**	**Day 113**	**Day 127**	**Day 141**	**Day 169**	**Day 197**	**Day 225**	**Day 253**	**See Table 5**
PK (3M)	X	X	X	X	X	X	X	X	X	X	X	X	
PK (1M)									X	X	X	X	
PD (E2, FSH and LH)											X		
AEs	X			X	X	X	X	X	X	X	X	X	X
Prior and concomitant medication/therapies	X			X	X	X	X	X	X	X	X	X	X

1M=triptorelin acetate PR 1-month; 3M=triptorelin pamoate PR 3-month; AE=adverse event; E2=oestradiol; FSH=follicle stimulating hormone; LH=luteinising hormone; PD=pharmacodynamics; PK=pharmacokinetics.

a assessments to be conducted with samples from the subjects in the full PK/PD subgroup (comprising up to 16 subjects receiving 3M and up to 16 subjects receiving 1M; to be enrolled at selected sites) only

b time windows for full PK/PD assessments will be defined in the Study Manual