**A PIVOTAL, MULTICENTER, NON-COMPARATIVE TRIAL ON THE CONTRACEPTIVE EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF LF111 (DROSPIRENONE 4.0 MG) DURING 13 CYCLES**

**Sponsor Project Code: CF111/303**

**Scope Project Code: 183LE07.MMB**

# STATISTICAL ANALYSIS PLAN

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## DOCUMENT REVISION HISTORY

Version Draft 0.1 (13-JAN-2017): Document created.

Version Draft 0.2 (27-FEB-2017): Document updated after sponsor comments on SAP version draft 0.1.

Version Draft 0.3 (10-MAY-2017):

| Section | Updates |
|---|---|
| 2.2.2 Secondary Efficacy Endpoints | Deleted sentence "Additionally, only evaluable cycles will be included in analysis.". |
| 3.1 Analysis Sets | Sites 104 and 120 were excluded from the main analysis. Analysis sets were corrected accordingly. |
| 3.1 Analysis Sets | Included Additional Analysis Set. |
| 4.6 Trial Periods | Added Baseline value definition. |
| 5.5 Efficacy Analysis | Added Confirmed and non-confirmed pregnancy definition. |
| 5.5 Efficacy Analysis | Evaluable cycle definition was adopted according to scenario IV. |
| 5.5.3 Additional Efficacy Analysis | Added new section "5.5.3 Additional Efficacy Analysis". |
| 5.7 Tolerability Analysis | Tables of bleeding and spotting episodes were merged into bleeding/spotting episodes tables. |
| 3.1 Analysis Sets | Rule for partial pregnancy determination date added. |

Version Draft 0.4 (11-SEP-2017):

| Section | Updates |
|---|---|
| 2.2.2 Secondary Efficacy Endpoints | Updated pregnancy ratio analysis definition. |
| 3.1 Analysis Sets | Safety tables will not consist of data from 104 and 120 sites. |
| 3.2 Subgroups | Overweight category was included. |
| 3.3 Data Review | Category of impact on cycles was deleted for criterions which cannot be checked through EDC data. |
| 5.2.1 Demographics | New age category was included. |
| 5.4.1 Exposure to IMP | Two consecutive missing entries was changes to gap between two active table intakes more than 48 hours. |
| 5.4.2 Efficacy Analysis | Definitions of Method failure pregnancy, Evaluable cycle and Perfect cycle was updated. |
| 5.6.1 Adverse Events | Safety tables will not consist of data from 104 and 120 sites. |

Version Draft 0.5 (10-NOV-2017):

| Section | Updates |
|---|---|
| 2.2.4 Tolerability Endpoints | Period 2-13 was added. |
| 3.3 Data Review | DRM listings were updated. |
| 4.6 Trial Periods | Definitions of Date of the first/last IMP intake and baseline value were updated. |
| 5.2.3 Medical History | Definition of current medical history condition was updated. |

Version Draft 0.6 (22-NOV-2017):

| Section | Updates |
|---|---|
| All | New tables were added:<br>15.1.4.1.2, 15.2.1.2.4, 15.2.1.2.5, 15.2.1.2.6, 15.2.1.2.7, 15.2.1.4.3, 15.2.1.4.4, 15.2.1.4.5, 15.2.1.4.6, 15.2.1.4.7, 15.2.1.4.8, 15.2.1.4.9, 15.3.1.8.1, 15.3.1.8.2, 15.3.1.8.3, 15.3.1.8.4, 15.3.1.8.5, 15.3.1.8.6, 15.3.6.1.2, 15.3.7.1.2, 15.3.8.1.2, 15.3.9.1.2, 15.4.4.1.1, 15.4.4.2.1, 15.4.4.3.1, 15.4.5.1.1, 15.4.6.1.1, 15.4.6.2.1, 15.4.6.3.1. |
| All | Analysis set for Table 15.1.3.1.1 and Listing 16.2.1.2, 16.2.1.14, 16.2.1.15 was changed. |
| 3.1 Analysis Sets | Definition of allocated to treatment set was deleted.<br>Definition of Full analysis and modified full analysis sets were changed. |
| 3.2 Subgroups | Median weight subgroup was updated. |
| 4.6 Trial Periods | Definitions of Date of the first/last IMP intake and baseline value were updated |
| 5.1.1 Disposition and Withdrawals | New subcategories ("IMP related", "non-IMP related" and "Uncategorized") were included. |

| | |
|---|---|
| | Analysis of withdrawn reasons were expanded. |
| 5.5 Efficacy Analysis | Suspected, subject confirmed not pregnant definition was added.<br>Non-confirmed pregnancy definition and perfect cycle definitions were updated.<br>Tables titles were updated. |

Version Draft 0.7 (08-DEC-2017):

| **Section** | **Updates** |
|---|---|
| All | New tables were added:<br>15.2.1.2.8_add, 15.2.1.2.9_add, 15.2.1.2.10_add, 15.2.1.2.11_add, 15.2.1.4.10_add, 15.2.1.4.11_add, 15.2.1.4.12_add, 15.2.1.4.13_add, 15.4.7.1.1_add, 15.4.7.2.1_add, 15.4.7.3.1_add.<br><br>New figures were added:<br>15.2.1.1_add, 15.2.1.2_add, 15.2.1.3_add, 15.2.1.4_add, 15.2.2.1_add, 15.2.2.2_add, 15.2.2.3_add, 15.2.2.4_add, 15.4.9.1_add, 15.4.9.2_add, 15.4.9.3_add, 15.4.10.1_add, 15.4.10.2_add, 15.4.11.1_add, 15.4.11.2_add |
| INTRODUCTION | Explanatory legend was included. |
| 2.2 Trial Endpoints | Additional endpoints were added. |
| 5.2.1 Demographics | Age subgroups were corrected. |
| 5.5 Efficacy Analysis | Exposure and perfect cycle definition was updated. |

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## LIST OF ABBREVIATIONS AND KEY TERMS

| Abbreviation | Description of abbreviation |
|---|---|
| ACE | Angiotensin-converting-enzyme |
| AE | Adverse event |
| AGUS | Atypical glandular cells of undetermined significance |
| ALAT | Alanine aminotransferase |
| ALP | Alkaline phosphatase |
| ASAT | Aspartate aminotransferase |
| ASC-H | Atypical squamous cells High-grade |
| ASC-US | Atypical squamous cells of undetermined significance |
| ATC | Anatomical Therapeutic Chemical |
| BMI | Body mass index |
| bpm | beats per minute |
| BUN | blood urea nitrogen |
| CI | Confidence interval |
| CIN | Cervical intraepithelial lesion |
| CPK | Creatine phosphokinase |
| DBP | Diastolic blood pressure |
| DMPA | Depot medroxyprogesterone acetate |
| DRM | Data review meeting |
| DRSP | Drospirenone |
| DVT | Deep vein thrombosis |
| eCRF | Electronic case report form |
| EDV | Early discontinuation visit |
| ES | Enrolled Set |
| MFAS | Modified Full analysis set |
| hCG | Human chorionic gonadotropin |
| HDL | High-density lipoprotein |
| HIV | Human immunodeficiency virus |
| HLGT | High level group term |
| HLT | High level term |
| HPV | Human papilloma virus |
| IMP | Investigational medicinal product |
| IUD | Intra-uterine device |
| LDH | Lactate dehydrogenase |
| LDL | Low-density lipoprotein |
| LGSIL | Low grade squamous intraepithelial lesion |
| LLT | Lowest level term |
| LOCF | Last observation carried forward |
| Max | Maximum |
| MCH | Mean corpuscular hemoglobin |
| MCV | Mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Min | Minimum |
| mmHg | Millimeters of mercury |
| n | Number |
| OTC | Over-the-counter |

| | |
|---|---|
| PE | Pulmonary embolism |
| PI | Pearl index |
| PPS | Per protocol set |
| PT | Preferred term |
| SAP | Statistical analysis plan |
| SAS | Statistical analysis system |
| SBP | Systolic blood pressure |
| SD | Standard deviation |
| SOC | System organ class |
| SS | Safety set |
| TEAE | Treatment emergent adverse event |
| TLFs | Tables, Listings and Figures |
| VTE | venous thromboembolism |
| WHO-DDE | World Health Organization-Drug Dictionary |

## INTRODUCTION

This statistical analysis plan (SAP) contains a more technical and detailed elaboration of the principal features of the statistical analyses as described in the clinical trial protocol and its amendments:

| | |
|---|---|
| Final Protocol: | 7 February 2014; Final Version 1.0 |
| Final Protocol: | 16 May 2014; Final Version 2.0 |
| Final Protocol: | 27 May 2014; Final Version 3.0 |
| Final Protocol: | 16 November 2015; Final Version 4.0 |

Protocol versions 1.0 and 2.0 were never effective.

The SAP includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data, and it is structured according to different data types.

Pharmacokinetic analysis will be described in a separate SAP.

All analysis data sets and statistical output will be produced by the statistics department at Kalvariju 300 Vilnius, Lithuania of Scope International AG using the SAS system version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA) [1].

## 1. FLOW CHART AND VISIT SCHEDULE

**Table 1: Schedule of Trial Procedures**

| **Visits** | **V1a (Screening)** | **V1b (Medication Dispensation)** | **V2** | **V3** | **V4** | **V5** | **V6/EDV** | **V7 (Follow-Up)** |
|---|---|---|---|---|---|---|---|---|
| **Medication cycle** | **3 to 4 weeks** | | **1** | **3** | **6** | **9[15]** | **13[1]** | **10 to 14 days after V6[2]** |
| | | | **Day 20 ± 2 of medication cycle** | | | | **Day 29 +2** | |
| Informed consent/assent | x | | | | | | | |
| Demography | x | | | | | | | |
| Medical and gynecological history[3] | x | | | | | | | |
| Prior medication/ contraceptive devices | x | | | | | | | |
| Concomitant medication/ contraceptive devices | x | | x | x | x | x | x | |
| Wish of pregnancy[13] | x | x | x | x | x | x | x | |
| Physical examination | x | | | | x | | x | |
| Vital signs[4, 11], body weight and height[7] | x | x | x | x | x | x | x | |
| Gynecological examination | x | | | | x | | x | |
| Transvaginal ultrasound | x | | | | | | x | |
| Cervical cytology (Pap smear) | x[19] | | | | | | x[19] | |
| Routine laboratory parameters[5] | x | | x[17] | x[10] | x | x[10] | x | |
| Pharmacokinetic analysis[12] | | | x | | x | | | |
| Urinalysis[6] | x | | | | x | | x | |
| Serum pregnancy test | x | | | | | | | |
| Urine pregnancy test[8] | | x | x | x | x | x | x | x |
| In-/exclusion criteria | x | x | | | | | | |
| Dispensing of IMP | | x[20] | x | x | x | x | | |
| Drug accountability | | | x[18] | x | x | x | x | |
| IMP acceptability[16] | | | | x | | | x | |
| Discuss consecutive contraceptive method | | | | | | x | | |
| Dispense/collect e-diary | | x[14] | | | | | x | |
| Review e-diary[9] | | | x | x | x | x | x | |
| Adverse events[9] | x | x | x | x | x | x | x | x |

1 Assessments are to be performed after completion of cycle 13 and also in case of early discontinuation.

2 The post treatment evaluation is to be performed by interviewing the subjects. Inquiries are to be made regarding menstrual cycle, possible return of fertility, and possible use of contraceptive.

3 Including check of venous thromboembolism (VTE) risk.

4 Blood pressure and pulse.

5 Laboratory parameters: hematology, biochemistry.

Hematology: hemoglobin, red blood cell count, mean corpuscular volume (MCV) and associated parameters, hematocrit, MCH, white blood cell count, differential white blood cell count including neutrophils, lymphocytes, eosinophils, basophils and monocytes, platelet count.

Biochemistry: sodium, potassium, chloride, creatinine, blood urea nitrogen (BUN), calcium, glucose, total proteins, albumin, total cholesterol (HDL, LDL cholesterol), triglycerides, gamma glutamyl transferase, total and direct bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), creatine phosphokinase (CPK), lactate dehydrogenase (LDH).

6 Urinalysis: leukocytes, nitrite, protein, glucose, ketones, blood, pH, urobilinogen, bilirubin, hemoglobin – dipstick.

7 V1a: Height has to be determined for all subjects. V1b to V6: Height has only to be determined in adolescent subjects (i.e. < 18 years of age).

8 In addition, each subject will perform a urine dipstick pregnancy test at home at the beginning of each new medication cycle. In case of an equivocal or positive urine pregnancy test, a quantitative serum pregnancy test has to be performed for confirmation.

9 On Day 10 + 2 days of each cycle, the subjects will be called by the site staff to collect information on adverse events which might have occurred, and to confirm e-diary compliance. Throughout each cycle, subjects will be called by site staff to review e-diary compliance as needed.

10 Only electrolytes.

11 Measurements of vital signs will be repeated twice with a break of one minute between them at each visit in sitting position, after at least five minutes of rest. The subject should not talk.

12 Two blood samples per visit will be collected to determine plasma concentrations of LF111 at Visits 2 and 4 and should ideally be one hour apart (between 45 and 120 minutes after the first sample) without a LF111 administration in between.

13 The subject will be asked if she has a wish of pregnancy at each visit. In case of a positive answer, the subject will be discontinued.

14 Once the e-diary has been assigned to a subject, a practice diary (training section in e-diary) has to be actively completed.

15 The investigator should arrange for the subject's further contraceptive treatment or make an appropriate referral, as needed, at V5. Consecutive contraceptives should be started after last IMP intake and should be used at least until V7/Follow-up. This arrangement is outside the trial and costs will not be covered by the Sponsor.

16 The subject will be asked by the investigator: Are you satisfied with this method? Answer options: strongly agree, agree, undecided, disagree, strongly disagree, no answer. Furthermore, for women who switched from another oral contraceptive method to the IMP will be asked by the investigator: How was your wellbeing during the intake of the IMP in comparison to the time when you took your former oral contraceptive? Answer options: better, unchanged, worse, no answer.

17 Serum potassium will only be evaluated for subjects that take medications that may increase serum potassium (ACE inhibitors, angiotensin – II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin and aldosterone antagonists).

18 Drug accountability will only be performed in case a subject is discontinued prematurely or the IMP was collected from the subject. Otherwise the IMP will be counted by the investigator or designee at each visit and will be documented in the source documents only.

19 Pap smear not performed in subjects < 21 years of age.

20 On anticipated start date of Cycle 1 +2 days, the subject will be called by the site staff to confirm start date of IMP and e-diary compliance.

# 2. OBJECTIVES AND DESIGN

## 2.1 Trial Objectives

### 2.1.1 Primary Objective

The primary objective of this trial is to demonstrate the contraceptive efficacy of LF111.

### 2.1.2 Secondary Objectives

The secondary objectives of this trial are to demonstrate the safety and tolerability of LF111 and to assess the pharmacokinetics of LF111.

## 2.2 Trial Endpoints

### 2.2.1 Primary Efficacy Endpoints

The primary efficacy endpoint will be the Pearl Index (PI) based on evaluable cycles in non-breastfeeding women aged ≤ 35 years (at the time of trial enrolment).

PI = number of pregnancies*1300/number of evaluable medication cycles

An evaluable cycle is a cycle with intercourse without back-up contraceptive at least once per month based on the electronic diary question 'Did you have sexual intercourse since the beginning of the cycle?' and will be included in the primary analysis. If the cycle is not evaluable but the subject became pregnant in this cycle, the cycle has to be included in the analysis.

Pregnancies following premature termination of IMP will be excluded from the calculations if the estimated date of conception occurs later than seven days after the last tablet intake (active or placebo).

Date of conception will be determined by using the following information:

1. Ultrasound (the date of conception must be based on the most accurate method i.e. the first trimester ultrasound. Subsequent ultrasounds will not be allowed to change dating based on this initial assessment).
2. Ultrasound (in case the first trimester ultrasound was not performed)
3. Quantitative β-hCG
4. Qualitative urine β-hCG determination
5. Estimation of gestational age based on pelvic and/or abdominal examination or pregnancy outcome
6. Investigator's estimation in the absence of the above criteria

Medication cycle will be defined as 28 days starting with the administration of the first tablet from the blister containing 28 tablets and ending with the last day of intake.

### 2.2.2 Secondary Efficacy Endpoints

Cycles of breastfeeding women will be excluded from the efficacy analyses but included in the analyses regarding safety and tolerability.

Secondary efficacy endpoints are:

- Pearl Index based on overall cycles (overall PI) in women aged ≤ 35 years

  PI based on overall cycles will include all pregnancies which will occur during the trial in women aged ≤ 35 years (at the time of trial enrollment).

- PI for method failures in women aged ≤ 35 years

  Method failures PI will include all pregnancies of women who used the IMP correctly. Pregnancies are to be excluded from the calculation if in medication cycles of conception or in the previous medication cycles depending on the date of conception:

  - not all active tablets are taken (based on returned medication, recordings in the e-diary and non-compliance based on DRSP levels, if necessary)

- there is a tablet free interval between the previous medication cycle and the medication cycle of conception
- vomiting or diarrhea is documented
- administration of prohibited prior or concomitant therapy as detailed in Section 10.7 of the Clinical Trial Protocol is documented

- Pregnancy ratio in women aged ≤ 35 years (Life table analysis)

  In addition to PI analysis, method failure life table analysis and life table analysis on evaluable cycles will be performed in women aged ≤ 35 years (at the time of trial enrollment) in order to have the pregnancy rate at each cycle and cumulative pregnancy rates for 6 and 13 cycles. For life table analysis on evaluable cycles, only medication cycles of non-breastfeeding women will be considered as evaluable as defined in 2.2.1 and will be included in analysis. If the cycle is not evaluable but the subject became pregnant in this cycle, the cycle has to be included in the analysis. All pregnancies following premature termination of IMP will not be included in calculations if they occur later than seven days after the last tablet intake (active or placebo). Method failure pregnancy rates similar to method failure PI will include only those cycles of women who use the IMP correctly and include only perfect medication cycles as described in Section 5.5 of non-breastfeeding women.

- Overall PI, PI for method failures, PI for evaluable cycles and pregnancy ratio (life table analysis) in all women

  All analyses described above in women aged ≤ 35 years (at the time of trial enrollment) will also be evaluated for the whole subject population. Included are only cycles of non-breastfeeding women with sexual activity without using back-up contraception.

- Overall PI, PI for method failures, PI for evaluable cycles and pregnancy ratio (life table analysis) in women aged > 35 years

  All analyses described above in women aged ≤ 35 years (at the time of trial enrollment) will also be evaluated for women aged > 35 years at study enrollment. Included are only evaluable cycles of non-breastfeeding women with sexual activity without using back-up contraception.

  Overall PI will be based on exposure cycles.

**Efficacy Endpoints in Addition to the Protocol**

- Overall PI based on only confirmed and on confirmed and suspected, non-confirmed pregnancies (with and without sites 104 and 120)

  Overall PI based on exposure cycles will be evaluated for the whole subject population. Included are only cycles of non-breastfeeding women. The overall PI will be evaluated based on only confirmed pregnancies and on confirmed and suspected, non-confirmed pregnancies and in- and excluding sites 104 and 120.

  All analyses described above will be evaluated in addition by BMI subgroup and by weight subgroup.

- PI for evaluable cycles in women aged ≤ 35 years in total and by BMI and weight groups (with and without sites 104 and 120) based on confirmed and on confirmed and suspected, non-confirmed pregnancies

  PI based on evaluable cycles will be evaluated in women aged ≤ 35 years. Included are only cycles of non-breastfeeding women. The PI will be evaluated based on only confirmed pregnancies and on confirmed and suspected, non-confirmed pregnancies and in- and excluding sites 104 and 120.

  All analyses described above will be evaluated in addition by BMI subgroup and by weight subgroup.

### 2.2.3 Safety Endpoints

Analysis of safety endpoints will be conducted using the SS only.

- AEs

  All AEs will be summarized by number and proportion of subjects and number of AEs. TEAEs will be summarized by calculating the number and percent of subjects with AEs by MedDRA primary system organ class (SOC) and preferred term (PT). Also, TEAEs will be summarized by severity and relationship to treatment. Number and percent of subjects with serious TEAEs, TEAEs leading to trial termination and TEAEs of special interest will be provided by MedDRA PT and SOC.

- Vital signs

  Summary statistics for absolute values and absolute change from V1a (baseline) will be provided for each visit (V1b to V6/EDV).

- Clinical laboratory parameters

  Laboratory parameters will be summarized by calculating summary statistics on the absolute values and on the change from V1a to V3, V4, V5 and V6. Shift tables will be provided to illustrate changes with respect to the laboratory normal ranges between V1a and V6/Early discontinuation visit (EDV). The number and percent of subjects with values outside the limits of clinical significance reference ranges will be summarized.

### 2.2.4 Tolerability endpoints

The tolerability endpoints are based on vaginal bleeding pattern and include the following variables:

Bleeding:

- Number of subjects with bleeding by treatment day, treatment cycle and reference period (summary of cycles 2-4, 5-7, 8-10, 11-13 and 2-13)
- Number of subjects with unscheduled bleeding days by treatment cycle and reference period
- Number of subjects with scheduled bleeding days by treatment cycle and reference period
- Number of subjects with prolonged bleeding >nine days/ >14 days by reference period
- Number of bleeding episodes during treatment and by reference period
- Number of days with bleeding by cycle and reference period
- Number of days with unscheduled bleeding by cycle and reference period
- Number of days with scheduled bleeding by cycle and reference period
- Mean length of bleeding episodes by cycle and reference period

Spotting:

- Number of subjects with spotting by treatment day, treatment cycle and reference period (summary of cycles 2-4, 5-7, 8-10, 11-13 and 2-13)
- Number of subjects with unscheduled spotting days by treatment cycle and reference period
- Number of subjects with scheduled spotting days by treatment cycle and reference period
- Number of subjects with prolonged spotting >nine days/ >14 days by reference period
- Number of spotting episodes during treatment and by reference period
- Number of days with spotting by cycle and reference period
- Number of days with unscheduled spotting by cycle and reference period
- Number of days with scheduled spotting by cycle and reference period
- Mean length of spotting episodes by cycle and reference period

Only cycles of women with complete and correct diary entries will be taken into account in the analysis.

All tolerability variables will be evaluated over 13 cycles.

Another tolerability endpoint is the IMP acceptability.

**Tolerability Endpoints in Addition to the Protocol**

In addition, tolerability endpoints that are based on vaginal bleeding pattern and on combined variables (bleeding/spotting) will be evaluated:

- Number of subjects with bleeding/spotting by treatment day, treatment cycle and reference period
- Number of subjects with unscheduled bleeding/spotting days by treatment cycle and reference period
- Number of subjects with scheduled bleeding/spotting days by treatment cycle and reference period
- Number of subjects with no bleeding/spotting days by treatment cycle and reference period
- Number of days with bleeding/spotting by cycle and reference period by BMI subgroup
- Number of days with unscheduled bleeding/spotting by cycle and reference period by BMI subgroup
- Number of days with scheduled bleeding/spotting by cycle and reference period by BMI subgroup
- Number of days with bleeding/spotting by cycle and reference period by weight subgroup
- Number of days with unscheduled bleeding/spotting by cycle and reference period by weight subgroup
- Number of days with scheduled bleeding/spotting by cycle and reference period by weight subgroup

### 2.2.5 Pharmacokinetic endpoints

Pharmacokinetic endpoint analysis will be described in a separate SAP.

## 2.3 Overall Trial Design

This trial is a prospective, multicenter, open-label, non-controlled trial in female subjects, age 15 or above who present to the clinic seeking contraception, who are postmenarcheal and premenopausal. Breastfeeding women are allowed to participate in the trial.

At V1a (screening), informed consent/assent will be obtained and the screening procedures will be performed. At V1b, after the results of the laboratory tests have confirmed the subject's eligibility, the subject will be provided with the investigational medicinal product (IMP) and an electronic diary and the subject will be instructed in their use. On anticipated start date of Cycle 1+2 days, the trial staff will call the subject for the confirmation of IMP start date. Afterwards, the subjects will attend Visits 2 to 5 at Day 20±2 of the 1st, 3rd, 6th and 9th cycle and Visit 6 at Day 29+2 of the 13th cycle. The follow-up (Visit 7) will take place 10-14 days after Visit 6. Once a month, on Day 10 (+ 2 days) of each cycle, the subjects will be contacted by the site staff to collect information on any adverse events which might have occurred.

The trial will include women who have never used hormonal contraceptives before consent/assent (naïve users), women who have not used hormonal contraceptives in the past three months before consent/assent or who have used hormonal contraceptives in the past but have a contraceptive-free time of less than three months before consent/assent (previous users) as well as women directly switching from another hormonal method (switchers). Women who have used hormonal contraceptives in the past but have a contraceptive-free time of less than three months before consent/assent are allowed to be included into the trial if they had at least one complete menstrual cycle before enrollment.

For naïve users and previous users, the first IMP intake will be on the first day of the next menstrual bleeding after Visit V1b. (If the menstrual bleeding starts in the evening, and the subject prefers to take her pill in the morning, then she may begin the first IMP intake the next day [Day 2 of the menstrual bleeding]). For a switcher, the first IMP intake will be on the day following the last active pill of the previous hormonal contraceptive. The subject is free to choose an intake time in the morning or evening

that suits her requirements. Breastfeeding women can start the first IMP any day starting six weeks after delivery.

### 2.4 Randomization

Not applicable. Subjects will be allocated to treatment only if they satisfy all the inclusion criteria and are not precluded from participation by any of the exclusion criteria.

### 2.5 Treatments

The study product is LF111, which consists of coated tablets containing 4.0 mg DRSP. One package includes 24 active (white) tablets followed by 4 placebo (green) tablets. The dose for each subject is one tablet per day. During each medication cycle, the subjects will take 24 active tablets (each containing 4.0 mg DRSP) followed by 4 placebo tablets.

### 2.6 Sample Size

At least 920 subjects will be allocated to treatment to have at least 5000 evaluable cycles for the PI calculation in non-breastfeeding women aged ≤ 35 years (at the time of trial enrollment). Additionally, a minimum of 75 subjects aged > 35 years will be allocated to treatment. The calculations are based on empirical values including firstly a rate of 24.8% of subjects using back-up contraception or not having intercourse. Secondly, 45% of subjects are assumed to drop out of the trial. The prime target is to collect at least 5000 evaluable cycles.

### 2.7 Blinding

Not applicable to this trial.

# 3. ANALYSIS SETS AND SUBGROUPS

## 3.1 Analysis Sets

As described in the "CF111303: Site 104: Addendum to Investigation Report Signed 18-August-2016 by Cristin Barrett, SCOPE CRA Manager", "CF111303: Site 120: Addendum to Serious Breach Reporting Form Signed 23-August-2016 by Amy O'Sullivan, SCOPE Project Manager" and sponsor letter "RE: Clinical Trial CF111-303: exclude data from analysis for sites 104 and site 120" data from sites 104 and 120 will not be included in any statistical summary or analysis tables. Data from these sites will only be included in the Appendix 4 tables (Tables 15.1.1.1.1, 15.1.2.1.1, 15.1.3.1.1, 15.2.1.2.5, 15.2.1.2.7, 15.2.1.4.3, 15.2.1.4.5, 15.2.1.4.7, 15.2.1.4.9, 15.2.3.1.1 and 15.2.3.1.2), Appendix 5 listings and Appendix 6 figures (Figures 15.1.1.1, 15.1.2.1).

The analyses will be based on the following analysis sets:

**Enrolled Set** (ES) will consist of all subjects who signed informed consent/assent.

**Safety Set** (SS) will consist of all subjects who:

- took at least one dose of IMP.

**Full Analysis Set** (FAS) will consist of all subjects who:

- took at least one dose of IMP;
- were not pregnant at the date of first IMP intake.

**Modified Full Analysis Set** (MFAS) will consist of all subjects who:

- took at least one dose of IMP;
- were not pregnant at the date of first IMP intake;
- were non-breastfeeding.

**Per Protocol Set** (PPS) will not be defined since PI will be calculated using three methods therefore protocol violations will be taken into account.

Data of centers 104 and 120 will be excluded for SS and FAS calculations. Data of these centers will also be excluded for MFAS calculations unless it will be specified in the header of the respective tables that data of these centers are included.

## 3.2 Subgroups

The following subgroups will be defined:

- Weight subgroups, defined as
  - < median weight of the safety set
  - ≥ median weight of the safety set
- Body mass index (BMI) subgroups, defined as
  - BMI < 30 $kg/m^2$
  - BMI ≥ 30 $kg/m^2$
  - 25 $kg/m^2$ < BMI < 30 $kg/m^2$ [1]
- Blood pressure subgroups, defined as
  - Systolic blood pressure (SBP) < 130 mmHg and diastolic blood pressure (DBP) < 85 mmHg
  - Systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg
- Race subgroups, defined as
  - American Indian or Alaska Native
  - Asian
  - Black or African-American

[1] 25 $kg/m^2$ < BMI < 30 $kg/m^2$ category is in addition to the protocol.

- Native Hawaiian or Other Pacific Islander
- White
- Other

- Ethnicity subgroups, defined as
  - Hispanic or Latino
  - Not Hispanic or Latino

### 3.3 Data Review

A data review meeting (DRM) will be held after database lock, prior to the final SAP and clinical database closure.

The following aims are defined for the DRM:

- to assign pregnancies to their category and cycle;
- to identify protocol deviations which may have impact on cycles;
- to assign subjects to each of the analysis sets;
- to check that there are no data issues that are outstanding or need resolution;
- to define complete and correct diary entry;
- to solve any outstanding issues in the SAP.

Appropriate trial team, including a physician, will review certain potential protocol deviations and will review relevant information regarding those deviations to determine whether each of them have an impact on a perfect cycle. Protocol deviations will be not categorized into major and minor rather they will be categorized according to their impact to the perfect medication cycle.

Inclusion criterion related deviations will be classified as follows:

| **Inclusion criteria**<br>(At Visit 1 (Screening) and at Visit 1b (Medication Dispensation), subjects must meet ALL of the following criteria) | **Impact on the cycle** | **DRM listing no.** |
|---|---|---|
| 1. Sexually active, postmenarcheal and premenopausal female subjects at risk of pregnancy with no upper age limit.<br><br>*Since Protocol Final Version 4.0*:<br>Sexually active, postmenarcheal and premenopausal female subjects at risk of pregnancy including breastfeeding women with no upper age limit. | Case by case decision | IN01, IN02 |
| 2. Female subjects at risk of pregnancy, between the ages of 15 and 17 (inclusive) provided that<br>• Applicable national, state and local laws allow subjects in this age group to consent to receive contraceptive services,<br>• All applicable laws and regulations regarding the informed consent of the subjects to participate in clinical trials are observed, and<br>• Subjects in this age group will also be encouraged to consistently and correctly use male condoms with every event of sexual intercourse.<br><br>*Since Protocol Final Version 4.0*:<br>Female subjects at risk of pregnancy, between the ages of 15 and 17 (inclusive) provided that<br>• Applicable national, state and local laws allow subjects in this age group to consent/assent to receive contraceptive services, and | All cycles | IN03 |

| | | |
|---|---|---|
| • All applicable laws and regulations regarding the informed consent/assent of the subjects to participate in clinical trials are observed. | | |
| 3. Regular cycles during the last six months before consent when not using hormonal contraception.<br><br>*Since Protocol Final Version 4.0*:<br>Regular cycles during the last six months before consent/assent when not using hormonal contraception. | Case by case decision | IN04 |
| 4. Menstruation restarted since last pregnancy (only applicable for women that were pregnant within the last six months), i.e., at least three complete menstrual cycle after delivery.<br><br>*Since Protocol Final Version 4.0*:<br>At least three complete menstrual cycles after delivery (only applicable for women who were pregnant within the last six months and for non-breastfeeding women). Breastfeeding women can be included six weeks after delivery irrespective of menstrual cycles post-delivery. | Case by case decision | IN05 |
| 5. At screening, maximum systolic blood pressure (median value of three values) less than or equal to 159 mm Hg and diastolic blood pressure (median value of three values) less than or equal to 99 mm Hg<br><br>*Since Protocol Final Version 4.0*:<br>At screening, maximum systolic blood pressure (median value of three values) ≤ 159 mmHg and diastolic blood pressure (median value of three values) ≤ 99 mmHg. | No impact | IN06 |
| 6. Be able and willing to provide written informed consent/assent, or assent if the subject is adolescent, prior to undergoing any trial related procedure. | - | - |
| 7. Willing to use trial contraception for thirteen 28-day cycles. | - | - |
| 8. Be willing to have intercourse each cycle of trial.<br><br>*Since Protocol Final Version 4.0*:<br>Be willing to have intercourse each cycle of trial without the need to use back-up contraceptive. | - | - |
| 9. Be willing to state that, to her best knowledge, her male sexual partner(s):<br>• Has not had a vasectomy or been previously diagnosed as infertile.<br>• Has not been previously diagnosed or suspected of human immunodeficiency virus (HIV) unless he has subsequently had a negative HIV test.<br>• Has not been known to have engaged in homosexual intercourse in the past five years unless he has had negative HIV test results since then.<br>• Has not shared injection drug needles in the past unless he has had a negative HIV test at least six weeks since last use. | - | - |
| 10. Agree not to participate in any other clinical trials during the course of this trial. | - | - |

Exclusion criterion related deviations will be classified as follows:

| **Exclusion criteria**<br>(Subjects are to be excluded from the trial for ANY ONE of the following reasons) | **Impact on the cycle** | **DRM listing no.** |
|---|---|---|
| 1. Pregnant or breastfeeding.<br><br>*Since Protocol Final Version 4.0*:<br>Pregnant. | All cycles | DRM01 |
| 2. Subject is known to or suspected of not being able to comply with the trial protocol, the use of trial medication or the use of the trial diary. | - | - |
| 3. History of infertility. | All cycles | EX02 |
| 4. Abnormal finding on pelvic, breast or ultrasound examination that in the investigator's opinion contraindicates participation in the trial. | Case by case decision | EX03 |
| 5. Unexplained amenorrhea. | Case by case decision | EX04 |
| 6. Known polycystic ovary syndrome. | Case by case decision | EX05 |
| 7. Abnormal Papanicolaou (Pap) smear (ASC-US or more severe finding) at screening. (Pap smear results from within the previous three months prior to consent are acceptable if the report is available to the trial investigator).<br><br>*Since Protocol Final Version 4.0*:<br>Women ≥ 21 years of age with a Papanicolaou (pap) smear reading LGSIL or higher at screening (or six months prior to screening date). Human papilloma virus (HPV) testing in subjects with atypical squamous cells of undetermined significance (ASC-US) can be used as an adjunctive test.<br>• Subjects with ASC-US can be included if they are negative for high-risk HPV strains.<br>• Subjects < 21 years of age do not require a pap smear. | Case by case decision | EX06 |
| 8. Known contraindication or hypersensitivity to ingredients or excipients of the IMP, including:<br>a. Renal insufficiency<br>b. Hepatic dysfunction<br>c. Adrenal insufficiency<br>d. Current or history of venous thrombophlebitis or thromboembolic disorders (venous thrombembolism; which includes deep vein thrombosis and pulmonary embolism)<br>e. Current or history of cerebral-vascular or coronary-artery disease<br>f. Valvular heart disease with thrombogenic complications<br>g. Diabetes with vascular involvement<br>h. Headaches with focal neurological symptoms<br>i. Major surgery with prolonged immobilization<br>j. Known or suspected carcinoma of the breast<br>k. Known or suspected sex-steroid sensitive malignancies<br>l. Undiagnosed abnormal genital bleeding | Case by case decision | EX07 |

| | | |
|---|---|---|
| m. Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use<br>n. Liver tumor (benign or malignant) or active clinically significant liver disease. | | |
| 9. Uncontrolled thyroid disorder (i.e., on stable dose of thyroid replacement for less than two months). | Case by case decision | EX08 |
| 10. Uncontrolled concomitant diseases (i.e., not on a stable treatment dose for at least two months). | Case by case decision | EX09 |
| 11. Evidence or history of alcohol, medication or drug abuse (within the last 12 months).<br><br>*Since Protocol Final Version 4.0*:<br>Evidence or history of alcohol, medication or drug abuse (within the last 12 months prior to consent/assent). | Case by case decision | EX10 |
| 12. Known inherited or acquired predisposition to VTE or ATE (e.g. factor $V_{Leiden}$, Prothrombin mutation, Antiphospholipid-antibodies) or bruising within the last 12 months prior to consent.<br><br>*Since Protocol Final Version 4.0*:<br>Known inherited or acquired predisposition to venous thromboembolism or arterial thromboembolism (e.g., factor $V_{Leiden}$, Prothrombin mutation, Antiphospholipid-antibodies) or bruising within the last 12 months prior to consent/assent. | No impact | EX11, EX12 |
| 13. Known or suspected HIV and/or hepatitis infection at screening. | All cycles | EX13 |
| 14. Received a dose of depot medroxyprogesterone acetate (DMPA or Depo-Provera) during the 10 months prior to consent, or received any combined injectable contraceptive (e.g., Cyclofem) during the six months prior to consent, or no spontaneous menses since last injection.<br><br>*Since Protocol Final Version 4.0*:<br>Received a dose of depot medroxyprogesterone acetate (DMPA or Depo-Provera®) during the 10 months prior to consent/assent, or received any combined injectable contraceptive (e.g., Cyclofem®) during the six months prior to consent/assent, or no spontaneous menses since last injection. | Case by case decision | EX14 |
| 15. Long-term treatment (longer than seven consecutive days) within a month prior to V1b of any medication that might interfere with the efficacy of hormonal contraceptives. Prohibited medication include:<br>a. Anticonvulsants (e.g. Phenytoin, carbamazepine, oxcarbazepine, topiramate, felbamate, primidone)<br>b. Barbiturates<br>c. Rifampin<br>d. Atorvastatin<br>e. Bosentan<br>f. Griseofulvin<br>g. Phenylbutazon<br>h. St. John's wort (hypericum perforatum)<br><br>*Since Protocol Final Version 4.0*: | Case by case decision | EX15 |

| | | |
|---|---|---|
| Long-term treatment (longer than seven consecutive days within a month prior to V1b) of any medication that might interfere with the efficacy of hormonal contraceptives. Prohibited medication include:<br>a. Anticonvulsants (e.g. phenytoin, carbamazepine, oxcarbazepine, topiramate, felbamate, primidone)<br>b. Barbiturates<br>c. Rifampin<br>d. Bosentan<br>e. Griseofulvin<br>f. St. John's wort (hypericum perforatum) | | |
| 16. Administration of human chorionic gonadotropin (hCG) or intake of co-medication containing hCG within a month prior to V1b. | Case by case decision | EX16 |
| 17. Progestin-releasing IUD or contraceptive implant received or in place within the last two months prior to consent.<br><br>*Since Protocol Final Version 4.0*:<br>Progestin-releasing intra-uterine device (IUD) or contraceptive implant received or in place within the last two months prior to consent/assent. | Case by case decision | EX17 |
| 18. Planned regular concomitant use of barrier contraceptive methods, spermicides, IUDs or other contraceptive measures (excepting occasional use for safety reasons, e. g. reduce risk of infection).<br><br>*Since Protocol Final Version 4.0*:<br>Planned regular concomitant use of barrier contraceptive methods, spermicides, IUDs or other contraceptive measures (excepting occasional use for safety reasons, e. g. reduce risk of infection). | - | - |
| 19. Evidence or history of clinically significant psychiatric illness or suicide risk. | No impact | EX18 |
| 20. Participation in another trial of an investigational drug or device parallel to the current trial, or less than 90 days before consent, or previous participation in the current trial and dispensed trial medication.<br><br>*Since Protocol Final Version 4.0*:<br>Participation in another trial of an investigational drug or device parallel to the current trial or less than 90 days before consent/assent, or previous participation in the current trial and dispensed trial medication. | - | - |
| 21. Subject is a member of the investigator's or Sponsor's staff or a relative or family member thereof. | - | - |
| 22. Any condition that, in the opinion of the investigator, may jeopardize protocol compliance or the scientific integrity of the trial. | - | - |

**Listings related to Inclusion/Exclusion criterions:**

| Number | Name |
|---|---|
| Listing IN01 | Subjects with Missing Age at Menarche |
| Listing IN02 | Sexually Non-Active Subjects. |
| Listing IN03 | Subjects with Missing Consent/Assent Date |
| Listing IN04 | Subjects with Non-Regular Menstrual Bleeding During the Last 6 Cycles Before Visit 1a |

| | |
|---|---|
| Listing IN05 | Non-Breastfeeding Subjects Who Had Delivery Within the Last Six Months or Breastfeeding Subjects Who Had Delivery Within Less than Six Weeks Before Visit 1a |
| Listing IN06 | Subjects with Maximum SBP ≥ 159 mmHg or DBP ≥ 99 mmHg at Visit 1a |
| Listing EX02 | Subjects with History of Infertility |
| Listing EX03 | Subjects with Abnormal Finding on Pelvic, Breast or Ultrasound Examination |
| Listing EX04 | Subjects with Unexplained Amenorrhea |
| Listing EX05 | Subjects with Known Polycystic Ovary Syndrome |
| Listing EX06 | Subjects ≥ 21 Years of Age with Abnormal Papanicolaou Smear Reading or Positive Human Papilloma Virus Test |
| Listing EX07 | Subjects with Known Contraindication or Hypersensitivity to Ingredients or Excipients of the IMP |
| Listing EX08 | Subjects with Uncontrolled Thyroid Disorder |
| Listing EX09 | Subjects with Uncontrolled Concomitant Diseases |
| Listing EX10 | Excessive Drinkers |
| Listing EX11 | Subjects with Known Inherited Predisposition to Thromboembolic Illness |
| Listing EX12 | Subjects with Acquired Predisposition to Thromboembolic Illness or Bruising Within the Last 12 Months Prior to Visit 1a |
| Listing EX13 | Subjects with Known or Suspected HIV and/or Hepatitis Infection at Visit 1a |
| Listing EX14 | Subjects Who Received a Dose of Depot Medroxyprogesterone Acetate During the 10 Months Prior to Visit 1a, or Received Any Combined Injectable Contraceptive During the 6 Months Prior to Visit 1a |
| Listing EX15 | Subjects with Long-Term Treatment of Any Medication That Might Interfere with the Efficacy of Hormonal Contraceptives Prior to Visit 1b |
| Listing EX16 | Subjects Who Received Human Chorionic Gonadotropin or Co-Medication Containing Human Chorionic Gonadotropin Within a Month Prior to V1b |
| Listing EX17 | Subjects with Progestin-Releasing Intra-Uterine Device or Contraceptive Implant Received or in Place within the Last 2 Months Prior to Visit 1a |
| Listing EX18 | Subjects with history of clinically significant psychiatric illness or suicide risk |

Additional trial conduct criteria deviations will be classified as follows:

| Number | Name |
|---|---|
| Listing DRM01 | Subjects Who Became Pregnant During the Study |
| Listing DRM02 | Cycles when Vomiting or Diarrhea is Documented |
| Listing DRM03 | Cycles with Administration of Prohibited Concomitant Therapy |
| Listing DRM04 | Subjects Who did not Meet Inclusion/Exclusion Criterions |
| Listing DRM05 | Listing and Chart with Treatment Cycles |
| Listing DRM06 | IMP Gaps of More Than 48 Hours |
| Listing DRM07 | Adverse Events of Special Interest |
| Listing DRM08 | Non-Complete or Non-Correct Treatment Diary Records |
| Listing DRM09 | Specification of Subject Withdrawn During Treatment |
| Listing DRM10 | Specification of Subject Withdrawn During Screening |
| Listing DRM11 | Protocol Deviation from eCRF |
| Listing DRM12 | Scenarios for first IMP intake preceding V1b |
| Listing DRM13 | Subjects with Partial Date of Last IMP Intake in eCRF |
| Listing DRM14 | Treatment Compliance According to Drug Accountability |
| Listing DRM15 | Subjects for Whom IMP Was Dispensed but Have No eDiary Records |
| Listing DRM16 | Subjects Who Have Cyst Larger Than 30 mm |

All decisions made during DRM will be documented in the DRM report.

# 4. GENERAL DEFINITIONS AND NAMING CONVENTIONS

In order to avoid ambiguity during the analysis, a number of definitions and conventions for data handling are described here.

## 4.1 General Methodology and Presentation of the Results

The default summary statistics for quantitative (continuous) variables will be

- the number of subjects with data available (n),
- mean,
- standard deviation (SD),
- median,
- minimum (Min) and maximum (Max),
- 1st and 3rd quartiles (Q1 and Q3) for continuous demographic and laboratory data.

Mean and median will be presented to one more decimal place than the raw value. SD will be reported to two decimal places greater than the original value. The minimum, maximum, 1st and 3rd quartiles and 95% CI values will be presented with the same decimal precision as the raw value.

For qualitative (categorical) variables, the frequency count (n) and percentage (%) of subjects with non-missing data per category will be presented. "Missing" classification without percentage will be presented only if missing data will be in respective category.

Percentage values will be presented to one decimal place.

The denominator used for calculation of the percentages will be specified in a footnote to the tables for clarification.

## 4.2 Statistical Output Layout

All titles and column headers (consisting of one or several words) will be capitalized; articles, prepositions, and conjunctions, and "To" in infinitives will not be capitalized, except they are at the beginning of titles or headers.

All pages will be numbered according to the table/listing/figure to which the page belongs to. Every table/listing/figure will be numbered from page 1, "Page X of Y" at the bottom of each page.

The definition of baseline and endpoint value will be described in a footnote in every TLF where applicable. Other important definitions will also be presented if necessary.

Dates will be listed in the format: <yyyy>-<mm>-<dd> (e.g. 2003-11-20). Times will be listed in the format: <hh>:<mm> (e.g. 09:15) or in the format <hh>:<mm>:<ss> if seconds are collected. When date and time are collected, these are listed in the format: <yyyy>-<mm>-<dd>T<hh>:<mm> (e.g. 2003-11-20T09:15), <yyyy>-<mm>-<dd>T<hh>, or <yyyy>-<mm>-<dd>T<hh>:<mm>:<ss>.

Partial missing dates will be listed in the format <yyyy>-<mm> (e.g. 2013-11) if only day is missing or in the format <yyyy> (e.g. 2013) if month and day are missing.

Missing data including missing dates or times will be displayed in listings as blank fields, unless otherwise specified.

Listings will be sorted by subject's number and visit number where applicable, unless specified otherwise.

## 4.3 Treatment Group Names and Labels

Since there is only one treatment group in this trial, statistical output will be presented only for the overall group. The labels to be used in the tables, listings and figures are defined in the table below.

| Treatment Group Description | Treatment Group Label, which will appear in the TLFs |
|---|---|
| DRSP 4.0 mg | DRSP 4.0 mg |

### 4.4 Visit Names and Labels

The names to be used in the analysis datasets and the labels to be used in the tables, listings and figures for the different trial visits are defined below.

| Visit number | Visit name | Visit label, which will appear in the TLFs |
|---|---|---|
| 10 | Visit 1a (V1a, Screening Visit) | Visit 1a or V1a |
| 11 | Visit 1b (V1b, Medication Dispensation Visit, as soon as the results of the routine laboratory tests from V1a are available) | Visit 1b or V1b |
| 20 | Visit 2 (V2, Day 20 ± 2 of Medication Cycle 1) | Visit 2 or V2 |
| 30 | Visit 3 (V3, Day 20 ± 2 of Medication Cycle 3) | Visit 3 or V3 |
| 40 | Visit 4 (V4, Day 20 ± 2 of Medication Cycle 6) | Visit 4 or V4 |
| 50 | Visit 5 (V5, Day 20 ± 2 of Medication Cycle 9) | Visit 5 or V5 |
| 60 | Visit 6 (V6, Day 29 + 2 of Medication Cycle 13) or EDV | Visit 6/EDV or V6/EDV |
| 70 | Visit 7 (V7, Follow-Up Visit, 10 to 14 days after V6) | Visit 7 (Follow-Up) or V7 (FU) |

### 4.5 Days Numbering

All assessment dates will be related to the first day of IMP intake. This first day of IMP intake is referred to as Day 1. Day -1 is the day that is preceding Day 1 and Day 0 will not be defined. The assessment series is built up so that Day -2 is the day before Day -1 in the pre-treatment period, and Day 2 the second day on trial medication, etc.

### 4.6 Trial Periods

**Date of the first IMP intake**

The date of the first IMP intake will be defined as the date of the first IMP intake recorded in the treatment diary.

If such date is not available and subject did not return all IMP pills, Visit 1b date will be taken into account.

**Date of the last IMP intake**

The date of last IMP intake will be defined as the date of the last IMP intake provided in the eCRF "Trial Termination" section.

If such date is incomplete the following will be imputed:

- The date of the last day of the month, if month and year is available but the day is missing.

If such date is not available or only year is provided, last date of IMP administration recorded in subject's diary will be taken into account. If last date of IMP administration recorded in subject's diary is not available and subject did not return all IMP pills, the subject's last visit date will be taken into account.

**Treatment period**

The treatment period is defined as the period from the first IMP intake up to the last IMP intake.

**Baseline value**

Baseline value for a variable will be defined as Visit 1a value.

**Absolute change**

Absolute change from Visit 1a to each visit will be calculated as

$$Absolute\ change\ from\ Baseline\ at\ Visit\ <X> = Value\ at\ Visit\ <X> - Baseline\ Value.$$

**Treatment cycle**

Treatment cycles will be defined as 28 days periods starting on the day of the first IMP intake from the blister containing 28 tablets. No more than 13 completed cycles will be used for analysis.

**Reference period**

The treatment period will be grouped into reference periods as:

- Cycles 2-4
- Cycles 5-7
- Cycles 8-10
- Cycles 11-13

**Overall period**

- Cycles 2-13

### 4.7 Visit Windows

No windowing will be done, that is, the data will be analyzed with the nominal visit numbers.

### 4.8 Complete and correct treatment diary records

Treatment diary records will be defined as correct and complete if the following information will be non-missing:

- Reference date (REFDTC),
- Vaginal bleeding or spotting (VAGBLEEX),
- Bleeding amount (BLEEDAMX).

### 4.9 Coding Systems and Conventions

#### 4.9.1 Coding of adverse events and medical history

Adverse event and medical history investigator terms are assigned to a lowest level term (LLT) and a preferred term (PT) and will be classified by high level term (HLT), high level group term (HLGT) and system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 17.0 [2].

#### 4.9.2 Coding of medications

Medications are classified according to active drug substance using the World Health Organization-Drug Dictionary (WHO-DD), version 2014 [3]. The WHO drug code has 11 digits. The generic name is defined by the first 6 of the 11 digits. In addition, the Anatomical Therapeutic Chemical (ATC) classes are assigned to the drug code. In this trial, ATC codes are defined to the 4$^{th}$ level.

### 4.10 Handling of Missing Data

Handling of missing data, if applicable, is discussed in the relevant sub-sections of Section 5.

# 5. STATISTICAL ANALYSIS: DEFINITIONS, DERIVATIONS, CALCULATIONS AND METHODOLOGY

## 5.1 Subjects Disposition

### 5.1.1 Disposition and Withdrawals

Disposition and withdrawal data will be collected at Visit 1a and Visit 6/EDV in eCRF and will include the following:

- Date of informed consent/assent;
- Reason for screening failure;
- Date of trial termination;
- Did the subject complete the trial as scheduled (yes, no);
- Reason for the premature trial termination;
- Date of last contact.

Screening failures will be subjects who have been enrolled in the trial (i.e. informed consent form signed/assent form signed), but discontinue the trial before first IMP intake due to the following reasons:

- Inclusion/exclusion criteria
- Withdrew consent
- Lost to follow-up
- Adverse event
- Other

One additional attempt to enroll a subject at screening may be permitted for screening failures if the subject fulfils the eligibility criteria. Both disposition events will be included in the analysis for subjects who were rescreened, i.e., the first disposition event (screening failure with reason) will be included into analysis.

The Trial Termination form must be completed for all subjects that have participated in at least one visit starting from Visit 1b, including subjects dropping out before any IMP intake. The subject information eCRF must be updated to indicate the subject status as Completed or Withdrawn.

Subjects may withdraw or may be withdrawn from the trial for the following reasons:

- at subject’s own request (withdrawal of consent/assent)
- if in the investigator’s opinion, for reasons of safety or ethics, continuation in the trial would be detrimental to the subject’s well-being
- major protocol deviations (rules to consider deviations as minor/major will be documented in the data review report)
- pregnancy
- wish for pregnancy
- development of an exclusion criterion if clinically significant
- adverse event
- at the specific request of the sponsor
- lost to follow-up
- other

In addition to protocol, withdrawn reasons (for subjects who were withdrawn) “At subject’s own request (withdrawal of consent)”, “If in the investigator’s opinion, for reasons of safety or ethics, continuation in the trial would be detrimental to the subject's well-being” and “Other” will be subcategorized as “IMP related”, “non-IMP related” and “Uncategorized” by data management. Final decision for subcategorization will be approved by sponsor.

Subjects' disposition table for withdrawals will include further summaries:

- Overall withdrawn reasons;
- Withdrawn reasons by visits;
- Withdrawn reasons by cycles;
- Withdrawn reasons by education level
- Withdrawn reasons by race;
- Withdrawn reasons by ethnicity;
- Withdrawn reasons by BMI groups.

Also, Subjects' disposition table without data from site 140 will be prepared.

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.1.1.1.1 | Analysis Sets | Enrolled | Number and percentage of subjects included into each analysis set will be presented. Percentage will be based on number of subjects in the ES. |
| Table 15.1.2.1.1 | Screen Failures | Enrolled | Number and percentage of subjects who were enrolled and failed screening will be presented and summarized by reasons associated with the discontinuation. Percentage will be based on number of subjects in the ES. |
| Table 15.1.3.1.1 | Reasons for Exclusion from Analysis Sets | Enrolled | Number and percentage of subjects excluded from SS, FAS and MFAS together with reason(s) for exclusion will be summarized. Percentage will be based on number of subjects in the ES. |
| Table 15.1.4.1.1 | Subjects' Disposition | Safety | The number and percentage of subjects who completed or discontinued study will be summarized. Reasons associated with the termination will be included. Percentage will be based on number of subjects in the SS. Data of centers 104 and 120 will be excluded. |
| Table 15.1.4.1.2 | Subjects' Disposition (Excluding Site 140) | Safety | The number and percentage of subjects who completed or discontinued study will be summarized excluded data from site 140. Reasons associated with the termination will be included. Percentage will be based on number of subjects in the SS. Data of centers 104 and 120 will be excluded. |
| Table 15.1.5.1.1 | Disposition by Attended Visit | Safety | The number and percentage of subjects attended at each visit will be summarized. Percentage will be based on number of subjects in the number of subjects in the SS. |
| Table 15.1.6.1.1 | Disposition by Sites | Safety | The number and percentage of subjects by sites will be summarized. Percentage will be based on number of subjects in the number of subjects in the SS. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.1.1 | Reasons for Exclusion from Analysis Sets | Enrolled | Subjects excluded from any analysis set and corresponding reasons for exclusion will be listed. |
| Listing 16.2.1.2 | Subject's Disposition | Safety | Disposition information from trial termination page will be listed. |
| Listing 16.2.1.3 | Subject Visits | Enrolled | Visits' dates will be listed for the subjects from ES. |

**Figures**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Figure 15.1.1.1 | Flow Chart of Subject Disposition | Enrolled | - |
| Figure 15.1.2.1 | Flow Chart of Analysis Sets | Enrolled | - |

### 5.1.2 Protocol Deviations

A Per-Protocol analysis will not be carried out and therefore no Per-Protocol population is defined. However, protocol deviations which may have impact on method failure PI will be reviewed during DRM and will be classified as according to their impact.

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.1.7.1.1 | Deviations Leading to Pregnancies Exclusion from the Method Failure Analysis | Modified Full Analysis | Number and percentage of pregnancies which were excluded from method failure analysis will be presented. Percentage will be based on total number of subjects in MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.1.7.1.2 | Deviations Leading to Cycles Exclusion from Analyses | Modified Full Analysis | Number and percentage of cycles which were excluded from some analysis will be presented. Percentage will be based on total number of cycles from subjects in MFAS. Data of centers 104 and 120 will be excluded. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.1.4 | Protocol Deviations Reported by Investigators | Enrolled | Protocol deviation from eCRF will be listed for the subjects from ES. |

### 5.1.3 Inclusion/Exclusion

The trial specific inclusion/exclusion criteria are presented in the Sections 9.2 and 9.3 of the Clinical Trial Protocol. For each criterion, as appropriate, a response of "Yes/No" is to be obtained at Visit 1a (Screening) and at Visit 1b (Medication Dispensation).

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.1.5 | Screening Failures | Enrolled | Subjects who discontinued the trial during the screening phase prior to enrolment to the treatment phase will be listed. Reasons associated with the discontinuation will be displayed. |
| Listing 16.2.1.6 | Inclusion Criteria Not Met and Exclusion Criteria Met | Enrolled | Listing of inclusion criteria which were not met and exclusion criteria which were met will be presented per subject. |

## 5.2 Demographic and Other Baseline Characteristics

### 5.2.1 Demographics

Demographic data collected at Visit 1a will include the following:

- Date of birth
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Highest level of education completed (No high school diploma, high school diploma or equivalent, some college, college degree or higher)
- Years of education completed for subjects who have no high school diploma
- Sexual activity.

**Age in years**

Age in years will be calculated as the difference between the date of birth and the date of informed consent/assent using the following SAS function:

$$Age = FLOOR(YRDIF(< date\ of\ informed\ consent >, < date\ of\ birth >, 'ACT/ACT'))$$

**Breastfeeding**

With Protocol Final Version 4.0, 16 November 2015 exclusion criteria have been changed and breastfeeding women were allowed to enter the study. Information on whether the subject is breastfeeding will be collected in the eCRF only on Protocol Final Version 4.0, 16 November 2015.

**Additional categories which will be presented in demographic and subgroup tables:**

- Breastfeeding status, defined as
  - Breastfeeding
  - Non-breastfeeding

- Age categories (the 1st rule), defined as
  - ≤35 years (at study enrollment)
  - >35 years (at study enrollment)
- Age categories (the 2nd rule), defined as
  - 15-17 years (at study enrollment)
  - 18-35 years (at study enrollment)
  - >35 years (at study enrollment)
- Non-breastfeeding women and race, defined as:
  - Non-breastfeeding women, American Indian or Alaska Native
  - Non-breastfeeding women, Asian
  - Non-breastfeeding women, Black or African-American
  - Non-breastfeeding women, Native Hawaiian or Other Pacific Islander
  - Non-breastfeeding women, White
  - Non-breastfeeding women, Other
- Non-breastfeeding women and BMI, defined as:
  - Non-breastfeeding women, BMI < 30 kg/m$^2$
  - Non-breastfeeding women, BMI ≥ 30 kg/m$^2$
  - Non-breastfeeding women, 25 kg/m$^2$ < BMI < 30 kg/m$^2$ [2]
- Sexual activity status, defined as:
  - Active
  - Non-active

**Baseline characteristics of the subjects include:**

- Body height (cm) at screening visit
- Body weight (kg) at screening visit
- BMI (kg/m$^2$) at screening visit
- Systolic blood pressure (mmHg) at screening visit
- Diastolic blood pressure (mmHg) at screening visit
- Pulse rate (bpm) at screening visit.

Median value from the 1st, 2nd and 3rd measurements for systolic, diastolic blood pressure and pulse rate will be summarized.

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.1.8.1.1 | Demographics | Safety | Default descriptive statistics for age (years) and years of education completed for subjects who have no high school diploma will be presented. Frequency tabulations for categories defined in Section 5.2.1 will be included. Percentage will be based on the number of subjects with non-missing data in the SS. Data of centers 104 and 120 will be excluded. |
| Table 15.1.8.1.2 | Demographics | Modified Full Analysis | Default descriptive statistics for age (years) and years of education completed for subjects who have no high school diploma will be presented. Frequency tabulations for categories defined in Section 5.2.1 will be included. Percentage will be based on the number of subjects with non-missing data in the MFAS. Data of centers 104 and 120 will be excluded. |

[2] 25 kg/m$^2$ < BMI < 30 kg/m$^2$ category is in addition to the protocol.

| | | | |
|---|---|---|---|
| Table 15.1.9.1.1 | Subgroups | Safety | Number and percentage of subjects included all subgroups from Section 3.2 will be provided. Percentage will be based on the number of subjects with non-missing data in the SS. Data of centers 104 and 120 will be excluded |
| Table 15.1.9.1.2 | Subgroups | Modified Full Analysis | Number and percentage of subjects included all subgroups from Section 3.2 will be provided. Percentage will be based on the number of subjects with non-missing data in the MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.1.10.1.1 | Baseline Characteristics at Screening | Safety | Body height, weight, BMI, systolic and diastolic blood pressure, pulse rate will be summarized for subjects in the SS. Data of centers 104 and 120 will be excluded. |
| Table 15.1.10.1.2 | Baseline Characteristics at Screening | Modified Full Analysis | Body height, weight, BMI, systolic and diastolic blood pressure, pulse rate will be summarized for subjects in the MFAS. Data of centers 104 and 120 will be excluded. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.1.7 | Demographics | Enrolled | Demographics will be listed for the subjects in the ES. |

### 5.2.2 Substance Use

Substance use for the subjects include:

- Smoking status at screening visit (Non-smoker, Current smoker, Ex-Smoker, Nicotine replacement therapy)
- Smoking start date
- Number of cigarettes per day
- Date of smoking cessation
- Alcohol status (Abstainer, Moderate drinker, Excessive drinker)

**Smoking duration (years)**

Smoking duration in years for current smokers will be calculated as the difference between the start date of smoking and the date of Visit 1a using the following SAS function:

$$INT(YRDIF(< smoking\ start\ date >, < Visit\ 1a\ date >, 'ACT/ACT'))$$

**Non-smoking duration (years)**

Non-smoking duration in years for ex-smokers will be calculated as difference between smoking cessation date and the date of Visit 1a using the following SAS function:

$$INT(YRDIF(< date\ of\ smoking\ cessation >, < Visit\ 1a\ date >, 'ACT/ACT'))$$

**Imputation of missing/incomplete dates:**

Incomplete dates will be imputed in the following way:

for incomplete/missing smoking start date:

- the first day of the month, if only day is missing
- 1st of January, if the year is available but the day and month are missing
- if date is completely missing smoking duration will be set to missing

for incomplete/missing smoking cessation date:

- the last day of the month if only the day is missing, unless the year and the month of smoking cessation and Visit 1a are the same then the day of Visit 1a will be imputed
- 31st of December if only the year is available unless Visit 1a was performed at the same year then the day of Visit 1a will be imputed
- for completely missing dates Visit 1a date will be imputed.

**Pack years smoking history:**

A pack year is a unit for measuring the amount a subject has smoked over a long period of time. It will be calculated as follows:

$$Number\ of\ pack\ years = \frac{number\ of\ cigarettes\ per\ day}{20\ (1\ pack\ has\ 20\ cigarettes)} \times smoking\ duration\ (years)$$

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.1.11.1.1 | Substance Use | Safety | Smoking duration, number of cigarettes per day, pack-years and non-smoking duration will be summarized as continuous data. Smoking status and alcohol status will be presented by means of default frequency tabulation. Percentage will be based on the number of subjects with non-missing data in the SS. Data of centers 104 and 120 will be excluded. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.1.8 | Substance Use | Enrolled | Information about subjects' smoking and alcohol use will be listed for the subjects in the ES. |

### 5.2.3 Medical History

Medical history includes any previous relevant illnesses, conditions and hospitalization during the last 6 months (longer in case of gynecological relevance) or any relevant ongoing (concomitant) diseases at Visit 1a.

Medical history of the subjects includes:

- Diagnosis
- Start date
- Stop date
- Ongoing tick box
- Treatment used (yes, no)

Medical history conditions will be classified as follows:

**Prior medical history conditions** are conditions which ended prior to Visit 1a.

**Current medical history conditions** are conditions which are ongoing at Visit 1a, i.e. "Ongoing" was ticked in eCRF at screening visit or stop date is after Visit 1a. In case of partial missing stop dates, a disease will be considered as ongoing at Visit 1a, unless the partial date information clearly indicates that the disease stopped prior to Visit 1a.

Also, medical history will be classified as **current medical history condition** if it stop date is completely missing and "Ongoing" status is not ticked.

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.1.12.1.1 | Prior Medical History Conditions | Safety | Prior medical history conditions will be summarized by displaying counts and percentages of subjects having at least one prior medical history condition and will be presented by SOC and PT. Subjects with two or more occurrences of the same disease/condition (as qualified by its PTs) will be counted only once for the respective PT. Percentage will be based on the number of subjects in the SS. Data of centers 104 and 120 will be excluded. |
| Table 15.1.12.2.1 | Current Medical History Conditions | Safety | Current medical history conditions will be summarized by displaying counts and percentages of subjects having at least one current medical history condition and will be presented by SOC and PT. Subjects with two or more occurrences of the same disease/condition (as qualified by its PTs) will be counted only once for the respective PT. |

| | | | |
|---|---|---|---|
| | | | Percentage will be based on the number of subjects in the SS. Data of centers 104 and 120 will be excluded. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.1.9 | Medical History | Enrolled | Medical history conditions will be listed for the subjects from ES. |

### 5.2.4 Gynecological History and VTE Risk Factors

Gynecological history of the subjects includes:

- Subject's age at menarche (years)
- Had the subject any deliveries (yes, no)
- Date of delivery
- Subject is currently breastfeeding tick
- Had the subject any miscarriages (yes, no)
- Date of miscarriage
- Had the subject any abortions (yes, no)
- Date of abortion

**Deliveries, miscarriages and abortions calcification**

Deliveries, miscarriages and abortions will be classified as follows:

- No delivery/miscarriage/abortion
- 1 delivery/miscarriage/abortion
- 2 deliveries/miscarriages/abortions
- 3 and more deliveries/miscarriages/abortions

**Number of VTE risk factors classification**

In addition to gynecological history findings a check of individual VTE risk factors will be performed at screening visit:

- Family history of thromboembolic illness (yes, no)
- Evidence of predisposing conditions for a vascular or metabolic disease (yes, no)
- Current smoker older than 35 years or non-smoker over 40 years old (yes, no)
- Body weight so that BMI > 30 kg/m$^2$ (yes, no)

Number of VTE risk factors per subject will be classified as follows:

- No risk factor
- 1 risk factor
- 2 risk factors
- 3 and more risk factors
- Missing

Missing category will be set if at least one of individual VTE risk factors will be missing.

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.1.13.1.1 | Gynecological History | Safety | Subject's age at menarche will be summarized as continuous data. Frequency tabulations for subject with any deliveries/miscarriages/abortions and subjects with "No", 1, 2 or 3 deliveries/miscarriages/ abortions will be presented. Percentage will be based on the number of subjects with non-missing data in the SS. Data of centers 104 and 120 will be excluded. |
| Table 15.1.14.1.1 | VTE Risk Factors | Safety | Frequency tabulations for subject with or without corresponding VTE risk factor and subjects with "No", 1, 2 |

| | | | |
|---|---|---|---|
| | | | or 3 corresponding number of VTE risk factors will be presented. Percentage will be based on the number of subjects with non-missing data in the SS. Data of centers 104 and 120 will be excluded. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.1.10 | Gynecological History | Enrolled | Gynecological history will be listed for the subjects from ES. |
| Listing 16.2.1.11 | VTE Risk Factors | Enrolled | VTE risk factors will be listed for the subjects from ES. |

### 5.2.5 Menstrual History

Menstrual history of the subjects includes (depending on the subject category some questions are not applicable):

- Subject category (Naive User, Previous User (No hormonal contraceptives for three months or more), Previous user (no hormonal contraceptives for less than three months), Switcher)

  Subcategories 'Prior users of progestin-only methods(s)', 'Prior user of combination hormonal contraception only' will be included for "Previous User" categories. Subcategories 'Prior users of progestin-only methods(s)', 'Prior user of combination hormonal contraception only' will be reviewed by Medical Monitor.
- Date of the first day of last menstrual bleeding before Visit 1a
- Was menstrual bleeding during last 6 cycles before V1a regular (yes, no)
- Mean intensity of menstrual bleeding during the last 6 cycles before Visit 1a (Light, Moderate, Heavy)
- Occurrence of spotting during the last 6 cycles before Visit 1a (yes, no)
- Occurrence of any unscheduled bleeding during the last 6 cycles before Visit 1a (yes, no)
- Intensity of unscheduled bleeding during the last 6 cycles before Visit 1a (Light, Moderate, Heavy)
- Occurrence of more than one menstrual bleeding absent during the last 6 cycles before Visit 1a (yes, no)
- Occurrence of at least one complete menstrual cycle before Visit 1a (yes, no)

**Time since last menstrual bleeding (days)**

Time since the last menstrual bleeding will be calculated as follows:

$$Time\ since\ last\ menstrual\ bleeding\ (days) = Date\ of\ Visit\ 1a - Date\ of\ the\ last\ day\ of\ last\ menstrual\ bleeding$$

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.1.15.1.1 | Menstrual History | Safety | Default summary statistics for time since last menstrual bleeding (days) will be summarized. Frequency tabulations for the rest of menstrual history variables will be presented. Percentage will be based on the number of subjects with non-missing data in the SS. Data of centers 104 and 120 will be excluded. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.1.12 | Menstrual History | | Menstrual history will be listed for the subjects from SS. |

## 5.3 Prior and Concomitant Medications, Contraceptive Devices

Medications in current use, relevant medications used within six months before consent/assent and newly started medications during the trial are to be documented including over-the-counter (OTC) medications and herbal remedies. In addition, changes of therapy (including changes of frequency) during the trial are to be documented in the eCRF.

The following information is collected:

- Drug unique number
- Medication (trade name)/Therapy/Device
- Indication (if medication is used as a contraceptive, a checkbox "Contraceptive (incl. device)" is checked)
- Dose per intake
- Units
- Frequency
- Route
- Start Date
- Stop Date/Ongoing (checkbox "Ongoing" is checked)

For subjects with at least 1 intake of IMP, medications and therapies are classified as 'prior' or 'concomitant' based on start/stop dates:

**Prior medications**

Prior medications are defined as medications which stopped before the first intake of IMP (Day 1 of Cycle 1).

**Concomitant medications**

Concomitant medications are defined as medications taken during the treatment period. This includes any medication when:

- the start date is on or after the first IMP intake and on or before the last IMP intake
  or
- the start date is before the first IMP intake and the stop date is after or on the first IMP intake day
  or
- the start date is before the first IMP intake and the tick box "Ongoing" is marked.

Where only partial dates are present, the month and/or year may be sufficient alone for classification of therapies but in cases where this is not possible it will be treated as concomitant.

The number and percentage of subjects with at least one medication within each ATC 2nd level subgroup and preferred drug name will be presented for the respective set. The ATC 2nd level subgroups and preferred drug name within ATC 2nd level subgroup will be ordered alphabetically.

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.1.16.1.1 | Prior Medications, Therapies and Contraception | Safety | The number and percentage of subjects taking prior medications will be presented by ATC 2nd level subgroup and preferred medication name for subjects in the SS. Data of centers 104 and 120 will be excluded. |
| Table 15.1.16.2.1 | Concomitant Medications, Therapies and Contraception | Safety | The number and percentage of subjects taking concomitant medications will be presented by ATC 2nd level subgroup and preferred medication name for subjects in the SS. Data of centers 104 and 120 will be excluded. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.1.13 | Prior and Concomitant Medications, Therapies and Contraception | Enrolled | Prior and concomitant medications, therapies and contraception will be listed for the subjects from ES. |

## 5.4 Exposure to IMP and Compliance

### 5.4.1 Exposure to IMP

Exposure data include:

- Date of the first IMP intake (subject's diary)
- Date of the last IMP intake
- Date of IMP dispensation
- Number of white tablets dispensed
- Number of green tablets dispensed
- Date of IMP collection
- Number of white tablets collected
- Number of green tablets collected
- Numbers of tablets taken (subject's diary)
- Date of IMP intake with time in hours and minutes (subject's diary)

Exposure data are derived from appropriate eCRF pages and diary. If the 1st regular IMP intake (variable PILDTC in subject's diary) was not entered, but the first IMP intake (variable BPILDTC in subject's diary) was entered then the 1st regular IMP intake will be derived from BPILDTC by adding time "T00:00".

**Derived variables:**

Overall treatment duration will be calculated as follows:

$$Overall\ treatment\ duration = Date\ of\ the\ last\ IMP\ intake - Date\ of\ the\ first\ IMP\ intake + 1.$$

Cumulative exposure will be categorized as:

- ≥ 28 days
- ≥ 84 days
- ≥ 168 days
- ≥ 252 days

**Missing Entries of IMP Intake in Treatment Diary**

Missing IMP intake entries will be classified as total number of missing entries and consecutive missing entries per respective cycle. Total and consecutive number of missing entries will be categorized as:

- Total missing entries over up to 13 cycles
  - 0-2 missing entries
  - 3-5 missing entries
  - 6-8 missing entries
  - 9 or more missing entries
- Total missing entries per separate cycle
  - 0 missing entries
  - 1 missing entries
  - 2 missing entries
  - 3 missing entries
  - 4 or more missing entries
- Active tablet free interval. Active tablet free interval is >48h tablet free interval during the second IMP intake till day 24 of each cycle or >144h interval between the last IMP intake and the first IMP intake in consecutive cycles. Tablet free interval calculation will not take into account cycle days 25-28.

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.1.17.1.1 | Exposure to Investigational Medicinal Product | Safety | Default summary statistics for the overall treatment duration in days will be presented. Default frequency tabulation for cumulative overall treatment duration will be displayed. Percentage will be based on the number of subjects in the SS. Data of centers 104 and 120 will be excluded. |
| Table 15.1.18.1.1 | Number of Subjects with at Least One Missing Entry of IMP Intake in Treatment Diary by Treatment Cycle and Overall | Safety | Numbers and percentages of subjects having at least one missing IMP intake will be presented. Number of missing IMP intakes will be presented by treatment cycle and overall. Percentage will be based on the number of subjects in respective cycle. Data of centers 104 and 120 will be excluded. |
| Table 15.1.19.1.1 | Number of Subjects with Gaps between Two Active Tablet Intakes of More Than 48/144 Hours by Treatment Cycle and Overall | Safety | Numbers and percentages of subjects having >48h (or 144h for the 1st IMP intake) active tablet free interval. Number of >48h (or 144h for the 1st IMP intake) active tablet free interval will be presented by treatment cycle and overall. Percentage will be based on the number of subjects in respective cycle. Data of centers 104 and 120 will be excluded. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.1.14 | Drug Accountability | Enrolled | Dispensation and collection of IMP will be listed for the subjects from ES. |

### 5.4.2 Compliance to IMP

Subject's compliance to the IMP will be checked throughout the trial by the investigator. It will be based on the dispensation and retrieval of medication and subjects' records in treatment diary.

Subjects will record their tablet intakes in the treatment diary.

The subject's overall treatment compliance according to eCRF records will be assessed by the tablet count and will be calculated according to the following formula:

$$Overall\ Compliance\ (eCRF)\ (\%) = \frac{Number\ of\ tablets\ dispensed - Number\ of\ tablets\ returned}{Overall\ treatment\ duration} \times 100\%.$$

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.1.20.1.1 | Compliance to Investigational Medicinal Product | Safety | Default summary statistics for overall treatment compliance according to eCRF records will be presented. Data of centers 104 and 120 will be excluded. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.1.15 | Treatment Compliance According to Drug Accountability | Enrolled | Treatment compliance will be listed for the subjects from ES. |

## 5.5 Efficacy Analysis

Primary and secondary efficacy analysis will be based on calculations of the PI in several different cases for non-breastfeeding women. The general formula of PI is

$$PI\ (< set\ of\ cycles >) = \frac{\sum on\text{-}drug\ pregnancy \in \{< set\ of\ cycles >\}}{\#\{< set\ of\ cycles >\}} \times 1300.$$

A two-sided 95% CI for the PI will be calculated assuming that events of pregnancy have a Poisson distribution. The CI will be calculated using the following equations from Gerlinger et al. [4]:

$$CI_{lower}\big(PI(< set\ of\ cycles >)\big) = \frac{1300}{\#\{< set\ of\ cycles >\}} \times CI_{lower}\big(\#\{pregnancy \in \{< set\ of\ cycles >\}\}\big),$$

$$CI_{upper}\big(PI(<set\ of\ cycles>)\big) = \frac{1300}{\#\{<set\ of\ cycles>\}} \times CI_{upper}\big(\#\{pregnancy \in \{<set\ of\ cycles>\}\}\big),$$

where

$$CI_{lower}\big(\#\{pregnancy \in \{<set\ of\ cycles>\}\}\big) = 0.5\chi^2\big(0.025; 2 \times \#\{pregnancy \in \{<set\ of\ cycles>\}\}\big),$$

$$CI_{upper}\big(\#\{pregnancy \in \{<set\ of\ cycles>\}\}\big) = 0.5\chi^2\big(0.025; 2 \times \#\{pregnancy \in \{<set\ of\ cycles>\}\} + 1\big),$$

where $\chi^2(\alpha; n) = \alpha\text{-}Quantile\ of\ \chi^2\text{-}distribution\ with\ parameter\ n.$

The following information from Pregnancy Notification forms will be taken:

- Subject ID number
- Estimated date of conception
- Method(s) Used to Estimate Conception Date

**Efficacy analysis definitions**

| Term | Definition |
|---|---|
| Confirmed pregnancy | Subject reported a positive urine home pregnancy test and the pregnancy was confirmed by qualitative urine pregnancy test (ß-hCG) and quantitative serum pregnancy test (ß-hCG). |
| Suspected, non-confirmed pregnancy | Subject reported a positive urine home pregnancy test but confirmatory qualitative urine pregnancy test (ß-hCG) and/or quantitative serum pregnancy test (ß-hCG) are missing. |
| Suspected, subject confirmed not pregnant | Subject reported a positive urine home pregnancy test but confirmatory qualitative urine pregnancy test (ß-hCG) and/or quantitative serum pregnancy test (ß-hCG) are negative. |
| On-drug pregnancy | An on-drug pregnancy includes all conceptions that occur from Day 1 (the initiation of study medication) through seven days after the final tablet (active or placebo) is taken. |
| Method failure pregnancy* | All on-drug pregnancies of women who used the IMP correctly.<br>Pregnancies are to be excluded from the calculation if in medication cycles of conception or in the previous medication cycles depending on the date of conception:<br>- not all active tablets are taken (based on returned medication, recordings in the e-diary and non-compliance based on DRSP levels, if necessary)<br>- there is an active tablet free interval between the previous medication cycle and the medication cycle of conception. Tablet free interval will be determined by record from treatment diary.<br>- vomiting or diarrhea is documented<br>- administration of prohibited prior or concomitant therapy as detailed in Section 10.7 of the Clinical Trial Protocol is documented |
| Exposure cycles | 28-day cycles, where at least one treatment diary entry of IMP intake is available. In addition, a cycle will be an exposure cycle if the subject become pregnant during this cycle regardless this cycle was a 28-day cycle or not. |
| Evaluable cycle | Cycles are exposure cycles with intercourse without back-up contraceptive at least once per cycle based on electronic diary question 'Did you have sexual |

| | |
|---|---|
| | intercourse since the beginning of the cycle?' and answered with: 'Yes I had sexual intercourse without additional contraception'.<br>Also, cycle is to be defined as evaluable if:<br>- Subject become pregnant at the respective cycle regardless back-up contraception was used or not.<br>- Cycle has missing answer about intercourse or answered "I had NO sexual intercourse at all" but subject become pregnant at the respective cycle.<br>Cycle will not be defined as evaluable if subject did not become pregnant and:<br>- The question was answered with 'Yes I had sexual intercourse with additional contraception'.<br>- Cycles with NO intercourse.<br>- Cycle has missing answer about intercourse. |
| Perfect cycle* | Evaluable cycles which have no:<br>- >48h tablet free interval during the second IMP intake till day 24 of each cycle or >144h interval between the last IMP intake and the first IMP intake in consecutive cycles. Tablet free interval calculation will not take into account cycle days 25-28.<br>- 4 or more days with forgotten tablets intake during 1-24 cycle days.<br>- Protocol deviations having effect on this cycle. |

* Method failure pregnancies will be only those which occurred during the perfect cycles, e.g., if pregnancy will contradict method failure definition then the cycle in which pregnancy occurred could not be called perfect cycle and vice versa.

### 5.5.1 Primary Efficacy Analysis

Analysis of the primary efficacy variable defined as PI based on evaluable cycles in non-breastfeeding women aged ≤ 35 years will be performed for the MFAS.

$$PI\ (evaluable\ cycles) = \frac{\sum on\text{-}drug\ pregnancy \in \{evaluable\ cycles\}}{\#\{evaluable\ cycles\}} \times 1300.$$

Respective two-sided 95% CI for PI based on evaluable cycles will be calculated according to formula in Section 5.5.

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.2.1.1.1 | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed on-drug pregnancies in the evaluable cycles will be presented. Number of evaluable cycles as well as PI and two-sided 95% CI will be presented. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |

### 5.5.2 Secondary Efficacy Analysis

Secondary Efficacy Analysis will be based on non-breastfeeding women. Also, analysis will be performed in BMI subgroups.

**Overall PI**

Overall PI will be calculated based on exposure cycles for all women, aged ≤ 35 years and aged > 35 years:

$$PI\ (exposure\ cycles) = \frac{\sum on\text{-}drug\ pregnancy \in \{exposure\ cycles\}}{\#\{exposure\ cycles\}} \times 1300.$$

Respective two-sided 95% CI for overall PI will be calculated according to formula in Section 5.5.

**PI for method failures**

PI for method failures will be calculated based on perfect cycles for all women, aged ≤ 35 years and aged > 35 years. Number of pregnancies will be calculated according to method failure definition:

$$PI\ (method\ failure) = \frac{\sum method\ failure\ pregnancy \in \{perfect\ cycles\}}{\#\{perfect\ cycles\}} \times 1300.$$

Respective two-sided 95% CI for PI for method failures will be calculated according to formula in Section 5.5.

**Evaluable cycles PI**

Evaluable cycles PI will be calculated based on evaluable cycles for all women and women aged > 35 years:

$$PI\ (evaluable\ cycles) = \frac{\sum on\text{-}drug\ pregnancy \in \{evaluable\ cycles\}}{\#\{evaluable\ cycles\}} \times 1300.$$

Respective two-sided 95% CI for PI based on evaluable cycles will be calculated according to formula in Section 5.5.

**Life table analysis for pregnancy rate**

Method failure life table analysis and life table analysis on evaluable cycles will be performed in all women, women aged ≤ 35 and > 35 years in order to have the pregnancy rate at each cycle and cumulative pregnancy rates for 6 and 13 cycles.

Cumulative pregnancy rate will be calculated by using the **PROC LIFETEST** procedure:

**PROC LIFETEST** DATA=<data set> METHOD=KM OUTSURV=CL CONFTYPE=LOG;
TIME <time variable>*< censorship flag>(1);
**RUN**;

The Kaplan-Meier method will be used to estimate the cumulative pregnancy ratio. Logarithmic transformation will be used for 95% CI of the pregnancy rate. The period from the start of treatment until the pregnancy will be the time variable in this analysis. Subjects who did not become pregnant will be censored at their time of the last intake of IMP.

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.2.1.2.1 | Overall Pearl Index in Non-Breastfeeding Women (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed on-drug pregnancies will be presented. Number of exposure cycles as well as PI and two-sided 95% CI will be presented. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.1.2.2 | Overall Pearl Index in Non-Breastfeeding Women Aged ≤ 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed on-drug pregnancies will be presented. Number of exposure cycles as well as PI and two-sided 95% CI will be presented. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.1.2.3 | Overall Pearl Index in Non-Breastfeeding Women Aged > 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed on-drug pregnancies will be presented. Number of exposure cycles as well as PI and two-sided 95% CI will be presented. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.1.2.4 _add | Overall Pearl Index in Non-Breastfeeding Women by BMI Subgroup (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed on-drug pregnancies will be presented. Number of exposure cycles as well as PI and two-sided 95% CI will be presented by BMI subgroup. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.1.2.5 _add | Overall Pearl Index in Non-Breastfeeding Women by BMI Subgroup (Only Confirmed Pregnancies, Including Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed on-drug pregnancies will be presented. Number of exposure cycles as well as PI and two-sided 95% CI will be presented by BMI subgroup. Table analysis will be based on MFAS. Data of centers 104 and 120 will be included. |

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| Table 15.2.1.2.6 _add | Overall Pearl Index in Non-Breastfeeding Women by BMI Subgroup (Confirmed and Suspected, Non-confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed and suspected, non-confirmed on-drug pregnancies will be presented. Number of exposure cycles as well as PI and two-sided 95% CI will be presented by BMI subgroup. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.1.2.7 _add | Overall Pearl Index in Non-Breastfeeding Women by BMI Subgroup (Confirmed and Suspected, Non-confirmed Pregnancies, Including Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed and suspected, non-confirmed on-drug pregnancies will be presented. Number of exposure cycles as well as PI and two-sided 95% CI will be presented by BMI subgroup. Table analysis will be based on MFAS. Data of centers 104 and 120 will be included. |
| Table 15.2.1.2.8 _add | Overall Pearl Index in Non-Breastfeeding Women by Weight Subgroup (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed on-drug pregnancies will be presented. Number of exposure cycles as well as PI and two-sided 95% CI will be presented by weight subgroup. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.1.2.9 _add | Overall Pearl Index in Non-Breastfeeding Women by Weight Subgroup (Only Confirmed Pregnancies, Including Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed on-drug pregnancies will be presented. Number of exposure cycles as well as PI and two-sided 95% CI will be presented by weight subgroup. Table analysis will be based on MFAS. Data of centers 104 and 120 will be included. |
| Table 15.2.1.2.10_add | Overall Pearl Index in Non-Breastfeeding Women by Weight Subgroup (Confirmed and Suspected, Non-confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed and suspected, non-confirmed on-drug pregnancies will be presented. Number of exposure cycles as well as PI and two-sided 95% CI will be presented by weight subgroup. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.1.2.11_add | Overall Pearl Index in Non-Breastfeeding Women by Weight Subgroup (Confirmed and Suspected, Non-confirmed Pregnancies, Including Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed and suspected, non-confirmed on-drug pregnancies will be presented. Number of exposure cycles as well as PI and two-sided 95% CI will be presented by weight subgroup. Table analysis will be based on MFAS. Data of centers 104 and 120 will be included. |
| Table 15.2.1.3.1 | Pearl Index for Method Failures in Non-Breastfeeding Women (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed pregnancies in the perfect cycles will be presented. Number of perfect cycles as well as PI and two-sided 95% CI will be presented. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.1.3.2 | Pearl Index for Method Failures in Non-Breastfeeding Women Aged ≤ 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed pregnancies in the perfect cycles will be presented. Number of perfect cycles as well as PI and two-sided 95% CI will be presented. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.1.3.3 | Pearl Index for Method Failures in Non-Breastfeeding Women Aged > 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed pregnancies in the perfect cycles will be presented. Number of perfect cycles as well as PI and two-sided 95% CI will be presented. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.1.4.1 | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed pregnancies in the evaluable cycles will be presented. Number of evaluable cycles as well as PI and two-sided 95% CI will be presented. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.1.4.2 | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged > 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed pregnancies in the evaluable cycles will be presented. Number of evaluable cycles as well as PI and two-sided 95% CI will be presented. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.1.4.3 _add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years (Only Confirmed Pregnancies, Including Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed on-drug pregnancies in the evaluable cycles will be presented. Number of evaluable cycles as well as PI and two-sided 95% CI will be presented. Table analysis will be based on MFAS. Data of centers 104 and 120 will be included. |

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| Table 15.2.1.4.4_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years (Confirmed and Suspected, Non-confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed and suspected, non-confirmed on-drug pregnancies in the evaluable cycles will be presented. Number of evaluable cycles as well as PI and two-sided 95% CI will be presented. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.1.4.5_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years (Confirmed and Suspected, Non-confirmed Pregnancies, Including Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed and suspected, non-confirmed on-drug pregnancies in the evaluable cycles will be presented. Number of evaluable cycles as well as PI and two-sided 95% CI will be presented. Table analysis will be based on MFAS. Data of centers 104 and 120 will be included. |
| Table 15.2.1.4.6_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years by BMI Subgroup (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed on-drug pregnancies in the evaluable cycles will be presented. Number of evaluable cycles as well as PI and two-sided 95% CI will be presented by BMI subgroup. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.1.4.7_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years by BMI Subgroup (Only Confirmed Pregnancies, Including Sites 104 and 120) | Modified Full analysis | Number and percentage confirmed of on-drug pregnancies in the evaluable cycles will be presented. Number of evaluable cycles as well as PI and two-sided 95% CI will be presented by BMI subgroup. Table analysis will be based on MFAS. Data of centers 104 and 120 will be included. |
| Table 15.2.1.4.8_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years by BMI Subgroup (Confirmed and Suspected, Non-confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed and suspected, non-confirmed on-drug pregnancies in the evaluable cycles will be presented. Number of evaluable cycles as well as PI and two-sided 95% CI will be presented by BMI subgroup. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.1.4.9_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years by BMI Subgroup (Confirmed and Suspected, Non-confirmed Pregnancies, Including Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed and suspected, non-confirmed on-drug pregnancies in the evaluable cycles will be presented. Number of evaluable cycles as well as PI and two-sided 95% CI will be presented by BMI subgroup. Table analysis will be based on MFAS. Data of centers 104 and 120 will be included. |
| Table 15.2.1.4.10_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years by Weight Subgroup (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed on-drug pregnancies in the evaluable cycles will be presented. Number of evaluable cycles as well as PI and two-sided 95% CI will be presented by weight subgroup. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.1.4.11_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years by Weight Subgroup (Only Confirmed Pregnancies, Including Sites 104 and 120) | Modified Full analysis | Number and percentage confirmed of on-drug pregnancies in the evaluable cycles will be presented. Number of evaluable cycles as well as PI and two-sided 95% CI will be presented by weight subgroup. Table analysis will be based on MFAS. Data of centers 104 and 120 will be included. |
| Table 15.2.1.4.12_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years by Weight Subgroup (Confirmed and Suspected, Non-confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed and suspected, non-confirmed on-drug pregnancies in the evaluable cycles will be presented. Number of evaluable cycles as well as PI and two-sided 95% CI will be presented by weight subgroup. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.1.4.13_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years by Weight | Modified Full analysis | Number and percentage of confirmed and suspected, non-confirmed on-drug pregnancies in the evaluable cycles will be presented. Number of evaluable cycles as well as PI and two-sided 95% CI will be presented by weight subgroup. |

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| | Subgroup (Confirmed and Suspected, Non-confirmed Pregnancies, Including Sites 104 and 120) | | Table analysis will be based on MFAS. Data of centers 104 and 120 will be included. |
| Table 15.2.2.1.1 | Overall Pregnancy Rate Life Table in Non-Breastfeeding Women (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Life table with the confirmed on-drug pregnancy rate at each cycle and cumulative pregnancy rates for 6 and 13 cycles will be presented. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.2.1.2 | Overall Pregnancy Rate Life Table in Non-Breastfeeding Women Aged ≤ 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Life table with the confirmed on-drug pregnancy rate at each cycle and cumulative pregnancy rates for 6 and 13 cycles will be presented. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.2.1.3 | Overall Pregnancy Rate Life Table in Non-Breastfeeding Women Aged > 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Life table with the confirmed on-drug pregnancy rate at each cycle and cumulative pregnancy rates for 6 and 13 cycles will be presented. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |
| Table 15.2.2.2.1 | Evaluable Cycles Pregnancy Rate Life Table in Non-Breastfeeding Women (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Life table with the evaluable cycle pregnancy rate at each cycle and cumulative pregnancy rates for 6 and 13 cycles will be presented. Table analysis will be based on MFAS and confirmed pregnancies. Data of centers 104 and 120 will be excluded. |
| Table 15.2.2.2.2 | Evaluable Cycles Pregnancy Rate Life Table in Non-Breastfeeding Women Aged ≤ 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Life table with the evaluable cycle pregnancy rate at each cycle and cumulative pregnancy rates for 6 and 13 cycles will be presented. Table analysis will be based on MFAS and confirmed pregnancies. Data of centers 104 and 120 will be excluded. |
| Table 15.2.2.2.3 | Evaluable Cycles Pregnancy Rate Life Table in Non-Breastfeeding Women Aged > 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Life table with the evaluable cycle pregnancy rate at each cycle and cumulative pregnancy rates for 6 and 13 cycles will be presented. Table analysis will be based on MFAS and confirmed pregnancies. Data of centers 104 and 120 will be excluded. |
| Table 15.2.2.3.1 | Method Failure Life Table in Non-Breastfeeding Women (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Life table with the perfect cycle pregnancy rate at each cycle and cumulative pregnancy rates for 6 and 13 cycles will be presented. Table analysis will be based on MFAS and confirmed pregnancies. Data of centers 104 and 120 will be excluded. |
| Table 15.2.2.3.2 | Method Failure Life Table in Non-Breastfeeding Women Aged ≤ 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Life table with the perfect cycle pregnancy rate at each cycle and cumulative pregnancy rates for 6 and 13 cycles will be presented. Table analysis will be based on MFAS and confirmed pregnancies. Data of centers 104 and 120 will be excluded. |
| Table 15.2.2.3.3 | Method Failure Life Table in Non-Breastfeeding Women Aged > 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Life table with the perfect cycle pregnancy rate at each cycle and cumulative pregnancy rates for 6 and 13 cycles will be presented. Table analysis will be based on MFAS and confirmed pregnancies. Data of centers 104 and 120 will be excluded. |
| Table 15.2.3.1.1 _add | Overall Pearl Index in Non-Breastfeeding Women (Confirmed and Suspected, Non-confirmed Pregnancies, Including Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed and suspected, non-confirmed on-drug pregnancies will be presented. Number of exposure cycles as well as PI and two-sided 95% CI will be presented. Table analysis will be based on MFAS. Data of centers 104 and 120 will be included. |
| Table 15.2.3.1.2 _add | Overall Pearl Index in Non-Breastfeeding Women (Only Confirmed Pregnancies, Including Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed on-drug pregnancies will be presented. Number of exposure cycles as well as PI and two-sided 95% CI will be presented. Table analysis will be based on MFAS. Data of centers 104 and 120 will be included. |
| Table 15.2.3.1.3 _add | Overall Pearl Index in Non-Breastfeeding Women (Confirmed and Suspected, Non-confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full analysis | Number and percentage of confirmed and suspected, non-confirmed on-drug pregnancies will be presented. Number of exposure cycles as well as PI and two-sided 95% CI will be presented. Table analysis will be based on MFAS. Data of centers 104 and 120 will be excluded. |

## Listings

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.2.1 | Pregnancy Determination | Enrolled | All on study pregnancies will be listed. |
| Listing 16.2.2.2 | Pregnancy Outcome | Enrolled | All on study pregnancies with the outcome results will be listed. |
| Listing 16.2.2.3 | Subjects' Decision to Become Pregnant | Enrolled | Information about subjects' decision to become pregnant will be listed. |

## Figures

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Figure 15.2.1.1_add | Overall Pearl Index in Non-Breastfeeding Women by BMI and Race (Black or African-American vs White) (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full Analysis | Diagram showing the PI and 95%CI of confirmed on-drug pregnancies will be presented by race and BMI subgroups. Data of centers 104 and 120 will be excluded. |
| Figure 15.2.1.2_add | Overall Pearl Index in Non-Breastfeeding Women by BMI and Race (Black or African-American vs White) (Only Confirmed Pregnancies, Including Sites 104 and 120) | Modified Full Analysis | Diagram showing the PI and 95%CI of confirmed on-drug pregnancies will be presented by race and BMI subgroups. Data of centers 104 and 120 will be included. |
| Figure 15.2.1.3_add | Overall Pearl Index in Non-Breastfeeding Women by BMI and Race (Black or African-American vs White) (Confirmed and Suspected, Non-confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full Analysis | Diagram showing the PI and 95%CI of confirmed and suspected, non-confirmed on-drug pregnancies will be presented by race and BMI subgroups. Data of centers 104 and 120 will be excluded. |
| Figure 15.2.1.4_add | Overall Pearl Index in Non-Breastfeeding Women by BMI and Race (Black or African-American vs White) (Confirmed and Suspected, Non-confirmed Pregnancies, Including Sites 104 and 120) | Modified Full Analysis | Diagram showing the PI and 95%CI of confirmed and suspected, non-confirmed on-drug pregnancies will be presented by race and BMI subgroups. Data of centers 104 and 120 will be included. |
| Figure 15.2.2.1_add | Overall Pearl Index in Non-Breastfeeding Women by BMI and Ethnicity (Only Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full Analysis | Diagram showing the PI and 95%CI of confirmed on-drug pregnancies will be presented by ethnicity and BMI subgroups. Data of centers 104 and 120 will be excluded. |
| Figure 15.2.2.2_add | Overall Pearl Index in Non-Breastfeeding Women by BMI and Ethnicity (Only Confirmed Pregnancies, Including Sites 104 and 120) | Modified Full Analysis | Diagram showing the PI and 95%CI of confirmed and suspected, non-confirmed on-drug pregnancies will be presented by ethnicity and BMI subgroups. Data of centers 104 and 120 will be included. |
| Figure 15.2.2.3_add | Overall Pearl Index in Non-Breastfeeding Women by BMI and Ethnicity (Confirmed and Suspected, Non-Confirmed Pregnancies, Excluding Sites 104 and 120) | Modified Full Analysis | Diagram showing the PI and 95%CI of confirmed and suspected, non-confirmed on-drug pregnancies will be presented by ethnicity and BMI subgroups. Data of centers 104 and 120 will be included. |
| Figure 15.2.2.4_add | Overall Pearl Index in Non-Breastfeeding Women by BMI and Ethnicity (Confirmed and Suspected, Non-confirmed Pregnancies, Including Sites 104 and 120) | Modified Full Analysis | Diagram showing the PI and 95%CI of confirmed on-drug pregnancies will be presented by ethnicity and BMI subgroups. Data of centers 104 and 120 will be excluded. |
| Figure 15.2.3.1_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women by BMI and Race (Black or African-American vs White) (Only Confirmed | Modified Full Analysis | Diagram showing the PI and 95%CI of confirmed on-drug pregnancies will be presented by race and BMI subgroups. Data of centers 104 and 120 will be excluded. |

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| | Pregnancies, Excluding Sites 104 and 120) | | |

## 5.6 Safety Analysis

Analysis of safety endpoints will be conducted using the SS only.

### 5.6.1 Adverse Events

AE data includes:

- AE ID number
- AE name
- Start date
- Stop date
- Severity (mild, moderate, severe)
- Outcome (recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, recovering/resolving, fatal, unknown)
- Action taken with IMP (dose not changed, drug interrupted, drug withdrawn, not applicable, unknown)
- Relationship to IMP (unrelated, unlikely, possible, probable, definite)
- Other actions (none, medication required, tests required, hospitalization required or prolonged, other)
- Serious (yes, no)

The maximum severity (intensity) of the AE will be categorized by the investigator as follows:

- **Mild**: a type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: a type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- **Severe**: a type of AE that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects clinical status. The event possesses a significant risk of harm to the research participant and hospitalization may be required.

AEs severity will be defined as "Unknown" if severity assessment is missing.

**Drug relationship of adverse events**

The relationship of an AE to the IMP is a clinical decision by the investigator based on all available information and is graded as follows:

- **Unrelated**: A clinical event with no evidence of any causal relationship.
- **Unlikely**: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
- **Possible**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Probable**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
- **Definite**: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically

plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Related AEs include the categories "possible", "probable" and "definite".

Unrelated AEs include the categories "unrelated" and "unlikely".

The relationship of an AE to the IMP will be defined as "Unknown" if relationship grade assessment is missing.

**Treatment Emergent Adverse Events**

An AE that emerges during treatment having been absent prior to treatment or worsens relative to the pre-treatment state is defined as treatment emergent adverse event (TEAE). All AEs with onset or worsening after first intake of IMP until 10 days after last intake of IMP are defined as treatment emergent.

Where only partial dates are present, the month and/or year may be sufficient alone for assignment of treatment emergent AEs but in cases where this is not possible these AEs will be considered as treatment emergent.

**Serious Adverse Events**

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect

**Adverse Events of Special Interest**

Adverse events of special interest will be defined as hyperkalemia and venous thromboembolism events. Hyperkalemia will be identified as AEs with preferred terms "Hyperkalaemia" and "Blood potassium increased". Venous thromboembolism will be identified as embolic and thrombotic venous events and assignments will be handled by Medical Monitors after database closure.

**Adverse events leading to trial termination**

Defined as those events where "Action taken with investigational medicinal product" is indicated as "drug withdrawn".

All AEs will be summarized by calculating the number and percent of subjects with AEs as well as number of events. TEAEs will be summarized by calculating the number and percent of subjects with AEs by preferred term and system organ class. Also, TEAEs will be summarized by severity and relationship to treatment. Number and percent of subjects with serious TEAEs, TEAEs leading to trial termination and TEAEs of special interest will be provided by MedDRA PT and SOC.

Summaries of AEs will be repeated for defined subgroups.

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.3.1.1.1 | Summary of Adverse Events | Safety | An overall summary of AEs will be provided for subjects in the SS. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.1.2 | Summary of Adverse Events by Weight Subgroup | Safety | An overall summary of AEs will be provided for subjects in the SS. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |

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| Table 15.3.1.1.3 | Summary of Adverse Events by BMI Subgroup | Safety | An overall summary of AEs will be provided for subjects in the SS. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.1.4 | Summary of Adverse Events by Blood Pressure Subgroup | Safety | An overall summary of AEs will be provided for subjects in the SS. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.1.5 | Summary of Adverse Events by Race Subgroup | Safety | An overall summary of AEs will be provided for subjects in the SS. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.1.6 | Summary of Adverse Events by Ethnicity Subgroup | Safety | An overall summary of AEs will be provided for subjects in the SS. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.2.1 | Incidence of TEAEs | Safety | The number and percentage of subjects reporting TEAEs will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.2.2 | Incidence of TEAEs by Weight Subgroup | Safety | The number and percentage of subjects reporting TEAEs will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.2.3 | Incidence of TEAEs by BMI Subgroup | Safety | The number and percentage of subjects reporting TEAEs will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.2.4 | Incidence of TEAEs by Blood Pressure Subgroup | Safety | The number and percentage of subjects reporting TEAEs will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.2.5 | Incidence of TEAEs by Race Subgroup | Safety | The number and percentage of subjects reporting TEAEs will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.2.6 | Incidence of TEAEs by Ethnicity Subgroup | Safety | The number and percentage of subjects reporting TEAEs will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.3.1 | Incidence of TEAEs by Relationship | Safety | The number and percentage of subjects reporting TEAEs by relationship to study medication will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.3.2 | Incidence of TEAEs by Relationship by Weight Subgroup | Safety | The number and percentage of subjects reporting TEAEs by relationship to study medication will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.3.3 | Incidence of TEAEs by Relationship by BMI Subgroup | Safety | The number and percentage of subjects reporting TEAEs by relationship to study medication will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.3.4 | Incidence of TEAEs by Relationship by Blood Pressure Subgroup | Safety | The number and percentage of subjects reporting TEAEs by relationship to study medication will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.3.5 | Incidence of TEAEs by Relationship by Race Subgroup | Safety | The number and percentage of subjects reporting TEAEs by relationship to study medication will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.3.6 | Incidence of TEAEs by Relationship by Ethnicity Subgroup | Safety | The number and percentage of subjects reporting TEAEs by relationship to study medication will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.4.1 | Incidence of TEAEs by Worst Severity | Safety | The number and percentage of subjects reporting TEAEs by worst severity will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.4.2 | Incidence of TEAEs by Worst Severity by Weight Subgroup | Safety | The number and percentage of subjects reporting TEAEs by worst severity will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |

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|---|---|---|---|
| Table 15.3.1.4.3 | Incidence of TEAEs by Worst Severity by BMI Subgroup | Safety | The number and percentage of subjects reporting TEAEs by worst severity will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.4.4 | Incidence of TEAEs by Worst Severity by Blood Pressure Subgroup | Safety | The number and percentage of subjects reporting TEAEs by worst severity will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.4.5 | Incidence of TEAEs by Worst Severity by Race Subgroup | Safety | The number and percentage of subjects reporting TEAEs by worst severity will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.4.6 | Incidence of TEAEs by Worst Severity by Ethnicity Subgroup | Safety | The number and percentage of subjects reporting TEAEs by worst severity will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.5.1 | Incidence of Serious TEAEs | Safety | The number and percentage of subjects reporting serious TEAEs will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.5.2 | Incidence of Serious TEAEs by Weight Subgroup | Safety | The number and percentage of subjects reporting serious TEAEs will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.5.3 | Incidence of Serious TEAEs by BMI Subgroup | Safety | The number and percentage of subjects reporting serious TEAEs will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.5.4 | Incidence of Serious TEAEs by Blood Pressure Subgroup | Safety | The number and percentage of subjects reporting serious TEAEs will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.5.5 | Incidence of Serious TEAEs by Race Subgroup | Safety | The number and percentage of subjects reporting serious TEAEs will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.5.6 | Incidence of Serious TEAEs by Ethnicity Subgroup | Safety | The number and percentage of subjects reporting serious TEAEs will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.6.1 | Incidence of TEAEs Leading to Trial Termination | Safety | The number and percentage subjects reporting TEAEs leading to trial termination will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.6.2 | Incidence of TEAEs Leading to Trial Termination by Weight Subgroup | Safety | The number and percentage of subjects reporting TEAEs leading to trial termination will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.6.3 | Incidence of TEAEs Leading to Trial Termination by BMI Subgroup | Safety | The number and percentage of subjects reporting TEAEs leading to trial termination will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.6.4 | Incidence of TEAEs Leading to Trial Termination by Blood Pressure Subgroup | Safety | The number and percentage of subjects reporting TEAEs leading to trial termination will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.6.5 | Incidence of TEAEs Leading to Trial Termination by Race Subgroup | Safety | The number and percentage of subjects reporting TEAEs leading to trial termination will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.6.6 | Incidence of TEAEs Leading to Trial Termination by Ethnicity Subgroup | Safety | The number and percentage of subjects reporting TEAEs leading to trial termination will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.7.1 | Incidence of TEAEs of Special Interest | Safety | The number and percentage of subjects reporting TEAEs of special interest will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |

| | | | |
|---|---|---|---|
| Table 15.3.1.7.2 | Incidence of TEAEs of Special Interest by Weight Subgroup | Safety | The number and percentage of subjects reporting TEAEs of special interest will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.7.3 | Incidence of TEAEs of Special Interest by BMI Subgroup | Safety | The number and percentage of subjects reporting TEAEs of special interest will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.7.4 | Incidence of TEAEs of Special Interest by Blood Pressure Subgroup | Safety | The number and percentage of subjects reporting TEAEs of special interest will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.7.5 | Incidence of TEAEs of Special Interest by Race Subgroup | Safety | The number and percentage of subjects reporting TEAEs of special interest will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.7.6 | Incidence of TEAEs of Special Interest by Ethnicity Subgroup | Safety | The number and percentage of subjects reporting TEAEs of special interest will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.8.1 | Incidence of Related Serious TEAEs | Safety | The number and percentage of subjects reporting related serious TEAEs will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.8.2 | Incidence of Related Serious TEAEs by Weight Subgroup | Safety | The number and percentage of subjects reporting related serious TEAEs will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.8.3 | Incidence of Related Serious TEAEs by BMI Subgroup | Safety | The number and percentage of subjects reporting related serious TEAEs will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.8.4 | Incidence of Related Serious TEAEs by Blood Pressure Subgroup | Safety | The number and percentage of subjects reporting related serious TEAEs will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.8.5 | Incidence of Related Serious TEAEs by Race Subgroup | Safety | The number and percentage of subjects reporting related serious TEAEs will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.1.8.6 | Incidence of Related Serious TEAEs by Ethnicity Subgroup | Safety | The number and percentage of subjects reporting related serious TEAEs will be summarized by PT nested within SOC. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.3.1 | Adverse Event: General | Enrolled | All AEs information will be listed. |
| Listing 16.2.3.2 | Adverse Event: MedDRA Coding | Enrolled | All AEs will be listed by preferred term nested within system organ class. |
| Listing 16.2.3.3 | Serious Adverse Event | Enrolled | All SAEs information will be listed. |
| Listing 16.2.3.4 | TEAEs Leading to Trial Termination | Enrolled | All TEAEs Leading to Trial Termination information will be listed. |
| Listing 16.2.3.5 | TEAEs of Special Interest | Enrolled | All TEAEs of Special Interest information will be listed. |

### 5.6.2 Vital Signs

Vital signs include blood pressure, pulse, height, body weight and BMI data.

Summary statistics for parameter values and absolute parameter change values from Baseline to Visit 6/EDV will be provided for each visit as described in Sections 4.1 and 4.6.

**Blood pressure and pulse**

Blood pressure and pulse data include:

- Time of first/second/third measurement
- Pulse (bpm)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)

Blood pressure and pulse will be measured in a sitting position at all visits from V1a to V6/EDV, after the subject has rested for at least five minutes.

Median value from the 1st, 2nd and 3rd measurements for systolic, diastolic blood pressure and pulse rate will be summarized in analysis tables. All values from the 1st, 2nd and 3rd measurements for systolic, diastolic blood pressure and pulse rate will be provided in a listing.

**Height, body weight and body mass index**

Height, body weight and body mass index data include:

- Weight (kg)
- Height (cm)
- Body mass index (kg/m$^2$)

At V1a, height will be measured in all subjects. At V1b to V6 height only has to be determined in adolescent subjects. Body weight will be measured at all visits from V1a to V6/EDV, lightly dressed and without shoes. The determined body weight has to be calculated as BMI. The BMI as a measure for the physical constitution of a ≥18-year-old subject is defined as follows:

$$BMI\ at\ Visit\ X\ (kg/m^2) = \frac{Body\ weight\ at\ Visit\ X\ (kg)}{(Body\ height\ at\ Visit\ 1a\ (cm)/100)^2}.$$

The BMI as a measure for the physical constitution of a <18-year-old subject is defined as follows:

$$\text{BMI at Visit X (kg/m}^2) = \frac{\text{Body weight at Visit X (kg)}}{(\text{Body height at Visit X (cm)}/100)^2}.$$

Summary of vital signs will be repeated for defined subgroups.

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.3.2.1.1 | Summary of Vital Signs | Safety | Vital signs parameters will be summarized descriptively including change from baseline at each visit where assessments were made. Data of centers 104 and 120 will be excluded. |
| Table 15.3.2.1.2 | Summary of Vital Signs by Weight Subgroup | Safety | Vital signs parameters will be summarized descriptively by weight subgroup including change from baseline at each visit where assessments were made. Data of centers 104 and 120 will be excluded. |
| Table 15.3.2.1.3 | Summary of Vital Signs by BMI Subgroup | Safety | Vital signs parameters will be summarized descriptively by BMI subgroup including change from baseline at each visit where assessments were made. Data of centers 104 and 120 will be excluded. |
| Table 15.3.2.1.4 | Summary of Vital Signs by Blood Pressure Subgroup | Safety | Vital signs parameters will be summarized descriptively by blood pressure subgroup including change from baseline at each visit where assessments were made. Data of centers 104 and 120 will be excluded. |
| Table 15.3.2.1.5 | Summary of Vital Signs by Race Subgroup | Safety | Vital signs parameters will be summarized descriptively by race subgroup including change from baseline at each visit where assessments were made. Data of centers 104 and 120 will be excluded. |
| Table 15.3.2.1.6 | Summary of Vital Signs by Ethnicity Subgroup | Safety | Vital signs parameters will be summarized descriptively by ethnicity subgroup including change from baseline at each visit where assessments were made. Data of centers 104 and 120 will be excluded. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.4.1 | Vital Signs (EN) | Enrolled | All vital signs records will be listed. |

### 5.6.3 Clinical Laboratory Evaluation

Clinical laboratory values are collected as described in Section 1. The following parameters are collected:

**Hematology**: hemoglobin, red blood cell count, mean corpuscular volume (MCV) and associated parameters, hematocrit, MCH, white blood cell count, differential white blood cell count including neutrophils, lymphocytes, eosinophils, basophils and monocytes, platelet count.

**Biochemistry**: sodium, potassium, chloride, creatinine, blood urea nitrogen (BUN), calcium, glucose, total proteins, albumin, total cholesterol (HDL, LDL cholesterol), triglycerides, gamma glutamyl transferase, total and direct bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), creatine phosphokinase (CPK), lactate dehydrogenase (LDH).

**Pregnancy tests**: serum β-hCG and urine dipstick tests.

**Urinalysis (dipstick test)**: leukocytes, nitrite, protein, glucose, ketones, blood, pH, urobilinogen, bilirubin, hemoglobin.

All laboratory test results are assigned an LNH classification according to whether the value is lower than (L), within (N) or higher than (H) the reference range for that parameter as provided by the corresponding laboratory. Clinical significance of laboratory values is evaluated by the investigator.

According to CRF investigator will evaluate only total cholesterol (not separate cholesterol fractions) deviation as clinically significant or not.

If both absolute and percent values of eosinophils, basophils, monocytes or neutrophils will be out of range then clinical significance evaluation will be assigned for absolute value of respective parameter.

Laboratory parameters will be summarized by calculating summary statistics on the absolute values and on the change from baseline V4 and V6/EDV (hematology and urinalysis variables) and from baseline to V3, V4, V5 and V6/EDV (biochemistry variables). The number and percent of subjects with values outside the limits of reference range will be summarized. Shift tables will be provided to illustrate changes with respect to the laboratory normal ranges between V1a and V4 and V6/EDV (hematology variables) and between V1a and V3, V4, V5 and V6/EDV (biochemistry variables).

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.3.3.1.1 | Summary of Clinical Laboratory Tests: Hematology | Safety | Default summary statistics of absolute and absolute change results at V1a, V4 and V6/EDV will be presented. Data of centers 104 and 120 will be excluded. |
| Table 15.3.3.1.2 | Summary of Clinical Laboratory Tests: Biochemistry | Safety | Default summary statistics of absolute and absolute change results at V1a, V3, V4, V5 and V6/EDV will be presented. Data of centers 104 and 120 will be excluded. |
| Table 15.3.3.1.3 | Summary of Clinical Laboratory Tests: Urinalysis dipstick | Safety | Number and percentage of subjects for each parameter based on the number of subjects with non-missing data at will be presented. Data of centers 104 and 120 will be excluded. |
| Table 15.3.3.1.4 | Clinical Laboratory Tests: Incidence of Hematology Abnormalities | Safety | Number and percentage of subjects for each parameter will be presented in normal, abnormal NCS and abnormal CS categories at specified visit. Percentage will be based on the number of subjects with non-missing data. Data of centers 104 and 120 will be excluded. |
| Table 15.3.3.1.5 | Clinical Laboratory Tests: Incidence of Biochemistry Abnormalities | Safety | Number and percentage of subjects for each parameter will be presented in normal, abnormal NCS and abnormal CS categories at specified visit. Percentage will be based on the number of subjects with non-missing data. Data of centers 104 and 120 will be excluded. |

| | | | |
|---|---|---|---|
| Table 15.3.3.1.6 | Clinical Laboratory Tests: Shift Table of Hematology Results | Safety | Number and percentage showing changes in the number and frequency of subjects with respect to the normal range between Visit 1a and V4, V6/EDV will be presented. Subjects with missing data will be presented as part of a "missing" category. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |
| Table 15.3.3.1.7 | Clinical Laboratory Tests: Shift Table of Biochemistry Results | Safety | Number and percentage showing changes in the number and frequency of subjects with respect to the normal range between Visit 1a and V2, V3, V4, V5 and V6/EDV will be presented. Subjects with missing data will be presented as part of a "missing" category. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.5.1 | Laboratory Data: Hematology | Enrolled | Values of laboratory tests will be listed. |
| Listing 16.2.5.2 | Laboratory Data: Biochemistry | Enrolled | Values of laboratory tests will be listed. Pregnancy test results will be listed in the separate listing. |
| Listing 16.2.5.3 | Laboratory Data: Urinalysis | Enrolled | Urinalysis dipstick data will be listed. Pregnancy test results will be listed in the separate listing. |
| Listing 16.2.5.4 | Laboratory Data: Pregnancy tests | Enrolled | Pregnancy test serum β-hCG and urine dipstick tests results will be listed. |

### 5.6.4 Physical Examination Findings

Physical examinations will be performed at V1a, V4 and V6/EDV and include the following data:

- Date of physical examination
- General appearance (normal, abnormal, not done)
- Ears, eyes, nose and throat (normal, abnormal, not done)
- Lungs/chest (normal, abnormal, not done)
- Heart (normal, abnormal, not done)
- Abdomen (normal, abnormal, not done)
- Pelvic (normal, abnormal, not done)
- Back (normal, abnormal, not done)
- Thyroid (normal, abnormal, not done)
- Lymph nodes (normal, abnormal, not done)
- Skin (normal, abnormal, not done)
- Extremities including an inspection of the lower extremities for deep vein thrombosis (normal, abnormal, not done)
- Other abnormal observations

Abnormal values are assessed as clinically significant or not clinically significant.

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.3.4.1.1 | Physical Examination | Safety | Number and percentage at each visit will be presented. Percentage will be based on the number of subjects with non-missing data. Data of centers 104 and 120 will be excluded. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.6.1 | Physical Examination | Enrolled | Physical examination results will be listed. |

### 5.6.5 Gynecological Examinations

#### 5.6.5.1 Gynecological Examination

Gynecological examinations will be performed at V1a, V4 and V6/EDV.

The gynecological examinations will be described by the following data:

- Date of gynecological examination
- External genitalia (normal, abnormal, not done)
- Speculum examination (normal, abnormal, not done)
- Palpation of the internal genitalia (normal, abnormal, not done)
- Breasts (normal, abnormal, not done)

Gynecological examination abnormal values are assessed as clinically significant or not clinically significant.

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.3.5.1.1 | Gynecological Examination | Safety | Number and percentage at each visit will be presented. Percentage will be based on the number of subjects with non-missing data. Data of centers 104 and 120 will be excluded. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.7.1 | Gynecological Examination | Enrolled | Gynecological examination results will be listed. |

#### 5.6.5.2 Transvaginal Ultrasound Examination

Transvaginal ultrasound examinations will be performed at V1a and V6/EDV. The transvaginal ultrasound examination data will be described by the following data:

- Date of ultrasound
- The reason why transvaginal ultrasound was not performed
- Uterus (normal, abnormal, not done)
- Endometrium (normal, abnormal, not done)
- Ovaries (normal, abnormal, not done)
- Were any follicles or cysts identified during the ultrasound procedure (yes, no)
- Diameter of largest follicle (Right ovary)
- Diameter of largest cyst (Right ovary)
- Diameter of largest follicle (Left ovary)
- Diameter of largest cyst (Left ovary)

Transvaginal ultrasound examination abnormal values are assessed as clinically significant or not clinically significant.

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.3.6.1.1 | Transvaginal Ultrasound Examination | Safety | Number and percentage at each visit will be presented. Percentage will be based on the number of subjects with non-missing data. Data of centers 104 and 120 will be excluded. |
| Table 15.3.6.1.2 | Shift Table for Transvaginal Ultrasound Examination | Safety | Number and percentage showing changes in the number and frequency of subjects with respect to the normal test between baseline and EDV, V6 and V6/EDV will be presented. Subjects with missing data will be presented as part of a "missing" category. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.7.2 | Transvaginal Ultrasound Examination | Enrolled | Transvaginal Ultrasound examination results will be listed. |

### 5.6.5.3 Dysmenorrhea Characteristic

Dysmenorrhea characteristic will be collected at V1a and V6 (or EDV) and include:

- Suffering from dysmenorrhea within the last 6 cycles before Visit 1a (yes, no)
- Suffering from dysmenorrhea since the previous assessment (yes, no)
- Intensity of dysmenorrhea (slight, moderate, heavy)
- Use of pain medication (yes, no)

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.3.7.1.1 | Dysmenorrhea Characteristic | Safety | Number and percentage at each visit will be presented. Percentage will be based on the number of subjects with non-missing data. Data of centers 104 and 120 will be excluded. |
| Table 15.3.7.1.2 | Shift Table for Dysmenorrhea | Safety | Number and percentage showing changes in the number and frequency of subjects with respect to dysmenorrhea between baseline and EDV, V6 and V6/EDV will be presented. Subjects with missing data will be presented as part of a "missing" category. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.7.3 | Dysmenorrhea Characteristic | Enrolled | Dysmenorrhea characteristic will be listed. |

### 5.6.5.4 Mastodynia/Mastalgia Characteristic

Mastodynia/Mastalgia characteristic will be collected at V1a and V6/EDV and include:

- Suffering from mastodynia/mastalgia within the last 6 cycles before Visit 1a (yes, no)
- Suffering from mastodynia/mastalgia since the previous assessment (yes, no)
- Intensity of mastodynia/mastalgia (slight, moderate, heavy)
- Use of pain medication (yes, no)

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.3.8.1.1 | Mastodynia/Mastalgia Characteristic | Safety | Number and percentage at each visit will be presented. Percentage will be based on the number of subjects with non-missing data. Data of centers 104 and 120 will be excluded. |
| Table 15.3.8.1.2 | Shift Table for Mastodynia/Mastalgia | Safety | Number and percentage showing changes in the number and frequency of subjects with respect to the suffering from mastodynia/mastalgia between baseline and EDV, V6 and V6/EDV will be presented. Subjects with missing data will be presented as part of a "missing" category. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.7.4 | Mastodynia/Mastalgia Characteristic | Enrolled | Mastodynia/Mastalgia characteristic will be listed. |

### 5.6.6 Cervical Cytology

Cervical cytology will be taken at V1a and V6/EDV and the findings will include:

- Date of cervical cytology assessment
- Cervical cytology results (Normal/Inflammatory, ASC-US, ASC-H and AGUS – cannot exclude high-grade disease or cancer, CIN1, CIN2, CIN3 – carcinoma in situ, Carcinoma in situ – Microinvasive carcinoma, Microinvasive carcinoma – Invasive carcinoma)
- HPV results (Negative, Positive)
- The reason, why cervical cytology was not assessed

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.3.9.1.1 | Summary of Cervical Cytology | Safety | Number and percentage at each visit will be presented. Percentage will be based on the number of subjects with non-missing data. Data of centers 104 and 120 will be excluded. |
| Table 15.3.9.1.2 | Shift Table for Cervical Cytology Test | Safety | Number and percentage showing changes in the number and frequency of subjects with respect to the normal between baseline and EDV, V6 and V6/EDV will be presented. Subjects with missing data will be presented as part of a "missing" category. Percentage will be based on SS. Data of centers 104 and 120 will be excluded. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.8.1 | Cervical Cytology Results | Enrolled | Cervical cytology results will be listed. |

## 5.7 Tolerability Analysis

The tolerability assessment includes the vaginal bleeding pattern and the IMP acceptability. Analysis of tolerability endpoints will be conducted using the FAS.

All tolerability variables will be evaluated over 13 cycles.

### 5.7.1 Bleeding Pattern

The number and rate of subjects with different bleeding and spotting patterns will be presented for each cycle. The Clopper-Pearson 95% CI for vaginal bleeding or spotting rate of subjects will be calculated using the **PROC FREQ** procedure:

```
PROC FREQ DATA=<data set>;
        BY <by variable>;
        TABLES <endpoint variable> / BINOMIAL;
RUN;
```

The following definitions will be applied:

**Episode of bleeding/spotting** – bleeding/spotting days bounded on either end by two days of no bleeding or spotting. Missing data will be considered as bleeding/spotting day if it is bounded on bleeding/spotting days or one days of no bleeding or spotting.

**Days of bleeding/spotting** – presence of bleeding/spotting on actual day.

**Scheduled bleeding/spotting** – any bleeding or spotting that occurs during hormone-free intervals (defined as Days 25-28 ± 1 day). Bleeding/spotting that starts during this period and continues for up to eight consecutive days is considered as scheduled bleeding/spotting.

If scheduled bleeding starts in Cycle X but ends in Cycle (X+1) then bleeding episode will be assigned to Cycle X.

Any bleeding or spotting that occurs during cycle Days [1-8) of the first treatment cycle and lasts up to 8 consecutive bleeding/spotting days will also be considered as scheduled bleeding days.

**Unscheduled bleeding/spotting** – any bleeding/spotting that occurs outside the time window defined for scheduled bleedings.

Cumulative rate of subjects with different bleeding and spotting patterns for reference periods (summary of cycles 2-4, 5-7, 8-10 and 11-13) will be provided. Cumulative rates only for reference periods will also be presented for number and percent of subjects with prolonged bleeding and spotting > 9 days/ > 14 days and the number of bleeding and spotting episodes.

Number and percent of days per cycle and reference period with bleeding and spotting, scheduled bleeding, unscheduled bleeding, scheduled spotting or unscheduled spotting and duration of scheduled bleeding, scheduled spotting, unscheduled bleeding and unscheduled spotting will be analyzed descriptively.

Cycles without consecutively missing diary entries and with less than five non-consecutive missing diary entries will be used in the bleeding pattern analysis.

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.4.1.1.1 | Number of Subjects with Bleeding by Treatment Day, Treatment Cycle and Reference Period | Full Analysis | Number and percentage of subjects in respective time point will be presented. Percentage will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.1.2.1 | Number of Subjects with Unscheduled Bleeding Days by Treatment Cycle and Reference Period | Full Analysis | Number and percentage of subjects in respective time point will be presented. Percentage will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.1.3.1 | Number of Subjects with Scheduled Bleeding Days by Treatment Cycle and Reference Period | Full Analysis | Number and percentage of subjects in respective time point will be presented. Percentage will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.1.4.1 | Number of Days with Bleeding by Cycle and Reference Period | Full Analysis | Number of days will be summarized as continuous data. Number of days will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.1.5.1 | Number of Days with Unscheduled Bleeding by Cycle and Reference Period | Full Analysis | Number of days will be summarized as continuous data. Number of days will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.1.6.1 | Number of Days with Scheduled Bleeding by Cycle and Reference Period | Full Analysis | Number of days will be summarized as continuous data. Number of days will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.2.1.1 | Number of Subjects with Spotting by Treatment Day, Treatment Cycle and Reference Period | Full Analysis | Number and percentage of subjects in respective time point will be presented. Percentage is based on subject with respective cycle available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.2.2.1 | Number of Subjects with Unscheduled Spotting Days by Treatment Cycle and Reference Period | Full Analysis | Number and percentage of subjects in respective time point will be presented. Percentage will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.2.3.1 | Number of Subjects with Scheduled Spotting Days by Treatment Cycle and Reference Period | Full Analysis | Number and percentage of subjects in respective time point will be presented. Percentage will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.2.4.1 | Number of Days with Spotting by Cycle and Reference Period | Full Analysis | Number of days will be summarized as continuous data. Number of days will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.2.5.1 | Number of Days with Unscheduled Spotting by Cycle and Reference Period | Full Analysis | Number of days will be summarized as continuous data. Number of days will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.2.6.1 | Number of Days with Scheduled Spotting by Cycle and Reference Period | Full Analysis | Number of days will be summarized as continuous data. Number of days will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |

| | | | |
|---|---|---|---|
| Table 15.4.3.1.1 | Number of Bleeding/Spotting Episodes During Treatment and by Reference Period | Full Analysis | Default descriptive statistics for number of bleeding/spotting episodes will be presented. Number of bleeding/spotting episodes will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.3.2.1 | Duration of Bleeding/Spotting Episodes by Cycle and Reference Period | Full Analysis | Default descriptive statistics for duration of bleeding/spotting episodes will be presented. Duration of bleeding/spotting episodes will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.3.3.1 | Number of Subjects with Prolonged Bleeding/Spotting >9 and >14 Days by Reference Period | Full Analysis | Number and percentage of subjects in respective time point will be presented. Percentage will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.4.1.1 _add | Number of Subjects with Bleeding/Spotting by Treatment Day, Treatment Cycle and Reference Period | Full Analysis | Number and percentage of subjects in respective time point will be presented. Percentage will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.4.2.1 _add | Number of Subjects with Unscheduled Bleeding/Spotting Days by Treatment Cycle and Reference Period | Full Analysis | Number and percentage of subjects in respective time point will be presented. Percentage will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.4.3.1 _add | Number of Subjects with Scheduled Bleeding/Spotting Days by Treatment Cycle and Reference Period | Full Analysis | Number and percentage of subjects in respective time point will be presented. Percentage will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.5.1.1 _add | Number of Subjects with no Bleeding/Spotting Days by Treatment Cycle and Reference Period | Full Analysis | Number and percentage of subjects in respective time point will be presented. Percentage will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.6.1.1 _add | Number of Days with Bleeding/Spotting by Cycle and Reference Period in BMI Groups | Full Analysis | Number of days will be summarized as continuous data. Number of days will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.6.2.1 _add | Number of Days with Unscheduled Bleeding/Spotting by Cycle and Reference Period in BMI Groups | Full Analysis | Number of days will be summarized as continuous data. Number of days will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.6.3.1 _add | Number of Days with Scheduled Bleeding/Spotting by Cycle and Reference Period in BMI Groups | Full Analysis | Number of days will be summarized as continuous data. Number of days will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.7.1.1 _add | Number of Days with Bleeding/Spotting by Cycle and Reference Period by Weight Subgroup | Full Analysis | Number of days will be summarized as continuous data. Number of days will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.7.2.1 _add | Number of Days with Unscheduled Bleeding/Spotting by Cycle and Reference Period by Weight Subgroup | Full Analysis | Number of days will be summarized as continuous data. Number of days will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |
| Table 15.4.7.3.1 _add | Number of Days with Scheduled Bleeding/Spotting by Cycle and Reference Period by Weight Subgroup | Full Analysis | Number of days will be summarized as continuous data. Number of days will be based on the number of subjects with respective cycles available. Data of centers 104 and 120 will be excluded. |

## Listings

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.9.1 | Treatment Diary | Full Analysis | Treatment diary records will be listed. |

## Figures

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Figure 15.4.1.1 | Subjects with Bleeding by Treatment Day | Full Analysis | Linear diagram showing the number of women reporting bleeding by study days during treatment period will be provided. Data of centers 104 and 120 will be excluded. |

| | | | |
|---|---|---|---|
| Figure 15.4.1.2 | Subjects with Bleeding by Treatment Cycle | Full Analysis | Linear diagram showing the number of women reporting bleeding by treatment cycle will be provided. Data of centers 104 and 120 will be excluded. |
| Figure 15.4.1.3 | Subjects with Bleeding by Reference Period | Full Analysis | Linear diagram showing the number of women reporting bleeding by reference period will be provided. Data of centers 104 and 120 will be excluded. |
| Figure 15.4.2.1 | Subjects with Scheduled and Unscheduled Bleeding Days by Treatment Cycle | Full Analysis | Histogram showing the number of women reporting scheduled and unscheduled bleeding days by Treatment cycle will be provided. Data of centers 104 and 120 will be excluded. |
| Figure 15.4.2.2 | Subjects with Scheduled and Unscheduled Bleeding Days by Reference Period | Full Analysis | Histogram showing the number of women reporting scheduled and unscheduled bleeding days by reference period will be provided. Data of centers 104 and 120 will be excluded. |
| Figure 15.4.4.1 | Scheduled and Unscheduled Bleeding Days by Treatment Cycle | Full Analysis | Histogram showing the number of bleeding days by cycle will be provided. Data of centers 104 and 120 will be excluded. |
| Figure 15.4.4.2 | Scheduled and Unscheduled Bleeding Days by Reference Period | Full Analysis | Histogram showing the number of bleeding days by reference period will be provided. Data of centers 104 and 120 will be excluded. |
| Figure 15.4.5.1 | Subjects with Spotting by Treatment Day | Full Analysis | Linear diagram showing the number of women reporting spotting by study days during treatment period will be provided. Data of centers 104 and 120 will be excluded. |
| Figure 15.4.5.2 | Subjects with Spotting by Treatment Cycle | Full Analysis | Linear diagram showing the number of women reporting spotting by treatment cycle will be provided. Data of centers 104 and 120 will be excluded. |
| Figure 15.4.5.3 | Subjects with Spotting by Reference Period | Full Analysis | Linear diagram showing the number of women reporting spotting by reference period will be provided. Data of centers 104 and 120 will be excluded. |
| Figure 15.4.6.1 | Subjects with Scheduled and Unscheduled Spotting Days by Treatment Cycle | Full Analysis | Histogram showing the number of women reporting scheduled and unscheduled spotting days by Treatment cycle will be provided. Data of centers 104 and 120 will be excluded. |
| Figure 15.4.6.2 | Subjects with Scheduled and Unscheduled Spotting Days by Reference Period | Full Analysis | Histogram showing the number of women reporting scheduled and unscheduled spotting days by reference period will be provided. Data of centers 104 and 120 will be excluded. |
| Figure 15.4.7.1 | Bleeding/Spotting Episodes by Reference Period | Full Analysis | Histogram showing the number of spotting episodes by reference period will be provided. |
| Figure 15.4.8.1 | Scheduled and Unscheduled Spotting Days by Treatment Cycle | Full Analysis | Histogram showing the number of spotting days by cycle will be provided. Data of centers 104 and 120 will be excluded. |
| Figure 15.4.8.2 | Scheduled and Unscheduled Spotting Days by Reference Period | Full Analysis | Histogram showing the number of spotting days by reference period will be provided. Data of centers 104 and 120 will be excluded. |
| Figure 15.4.9.1_add | Subjects with Bleeding/Spotting by Treatment Day | Full Analysis | Linear diagram showing the number of women reporting bleeding/spotting by study days during treatment period will be provided. Data of centers 104 and 120 will be excluded. |
| Figure 15.4.9.2_add | Subjects with Bleeding/Spotting by Treatment Cycle | Full Analysis | Linear diagram showing the number of women reporting bleeding/spotting by treatment cycle will be provided. Data of centers 104 and 120 will be excluded. |
| Figure 15.4.9.3_add | Subjects with Bleeding/Spotting by Reference Period | Full Analysis | Linear diagram showing the number of women reporting bleeding/spotting by reference period will be provided. Data of centers 104 and 120 will be excluded. |
| Figure 15.4.10.1_add | Subjects with Scheduled and Unscheduled Bleeding/Spotting Days by Treatment Cycle | Full Analysis | Histogram showing the number of women reporting scheduled and unscheduled bleeding/spotting days by Treatment cycle will be provided. Data of centers 104 and 120 will be excluded. |
| Figure 15.4.10.2_add | Subjects with Scheduled and Unscheduled Bleeding/Spotting Days by Reference Period | Full Analysis | Histogram showing the number of women reporting scheduled and unscheduled bleeding/spotting days by reference period will be provided. Data of centers 104 and 120 will be excluded. |
| Figure 15.4.11.1_add | Scheduled and Unscheduled Bleeding/Spotting Days by Treatment Cycle | Full Analysis | Histogram showing the number of bleeding/spotting days by cycle will be provided. Data of centers 104 and 120 will be excluded. |

| | | | |
|---|---|---|---|
| Figure 15.4.11.2_ add | Scheduled and Unscheduled Bleeding/Spotting Days by Reference Period | Full Analysis | Histogram showing the number of bleeding/spotting days by reference period will be provided. Data of centers 104 and 120 will be excluded. |

### 5.7.2 IMP Acceptability

IMP acceptability will be summarized by default frequency tabulation. Shift tables will be provided to illustrate change from V3 to V6/EDV. Additionally, for subjects who switched from another oral contraceptive to the study medication default frequency tables will be summarized to present change of subject wellbeing.

**Tables**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Table 15.4.7.1.1 | IMP Acceptability Assessment | Full Analysis | Number and percentage will be presented. Percentage will be based on the number of subjects with non-missing data. |
| Table 15.4.7.2.1 | Shift table for IMP Acceptability Assessment | Full Analysis | Number and percentage showing changes between Visit 3 and Visit 6/EDV will be presented. Percentage will be based on FAS. |

**Listings**

| No. | Name | Analysis set | Comments |
|---|---|---|---|
| Listing 16.2.10.1 | IMP Acceptability Assessment | Full Analysis | IMP acceptability assessment records will be listed. |

## 6. INTERIM ANALYSIS

No interim analysis is planned.

## 7. REFERENCES

1. SAS® Institute Inc., Cary, North Carolina, United States of America, Version 9.4.
2. MedDRA – Medical Dictionary for Regulated Activities. International Federation of Pharmaceutical Manufacturers Associations (IFPMA), c/o TRW, VAR1/8A/MSSO, 12011 Sunset Hills Road, Reston, VA 20190-3285, USA, Version 17.0, 1 March 2014.
3. WHO – Drug Dictionary. World Health Organization Collaborating Center for International Drug Monitoring, P.O. Box 26, S-751 03 Uppsala, Sweden, version 2014.
4. Gerlinger C et al. Recommendation for confidence interval and sample size calculation for the Pearl Index. Eur J Contracept Reprod Health Care. 2003; 8:87-92.

# 8. APPENDICES

## 1. Specification of Tables

## 2. Specification of Listings

## 3. Specification of Figures

## 4. Tables

Appendix tables defined below will be provided in separate .rtf files for each output.

| Seq. No | Table No and Title | | Output file name |
|---|---|---|---|
| **Baseline Characteristics** | | | |
| 1. | Table 15.1.1.1.1 | Analysis Sets – Enrolled Set | T15_01_01_01_01_anal_sets_es |
| 2. | Table 15.1.2.1.1 | Screen Failures – Enrolled Set | T15_01_02_01_01_scr_fail_es |
| 3. | Table 15.1.3.1.1 | Reasons for Exclusion from Analysis Sets – Enrolled Set | T15_01_03_01_01_excl_anal_es |
| 4. | Table 15.1.4.1.1 | Subjects' Disposition – Safety Set | T15_01_04_01_01_dispos_ss |
| 5. | Table 15.1.4.1.2 | Subjects' Disposition (Excluding Site 140) – Safety Set | T15_01_04_01_02_dispos_wo140_ss |
| 6. | Table 15.1.5.1.1 | Disposition by Attended Visit – Safety Set | T15_01_05_01_01_dispos_visit_ss |
| 7. | Table 15.1.6.1.1 | Disposition by Sites – Safety Set | T15_01_06_01_01_dispos_sites_ss |
| 8. | Table 15.1.7.1.1 | Deviations Leading to Pregnancies Exclusion from the Method Failure Analysis – Modified Full Analysis Set | T15_01_07_01_01_dev_met_fail_mfas |
| 9. | Table 15.1.7.1.2 | Deviations Leading to Cycles Exclusion from Analyses – Modified Full Analysis | T15_01_07_01_02_dev_cyc_mfas |
| 10. | Table 15.1.8.1.1 | Demographics – Safety Set | T15_01_08_01_01_demo_ss |
| 11. | Table 15.1.8.1.2 | Demographics – Modified Full Analysis Set | T15_01_08_01_02_demo_mfas |
| 12. | Table 15.1.9.1.1 | Subgroups – Safety Set | T15_01_09_01_01_subgr_ss |
| 13. | Table 15.1.9.1.2 | Subgroups – Modified Full Analysis Set | T15_01_09_01_02_subgr_mfas |
| 14. | Table 15.1.10.1.1 | Baseline Characteristics at Screening – Safety Set | T15_01_10_01_01_base_char_ss |
| 15. | Table 15.1.10.1.2 | Baseline Characteristics at Screening – Modified Full Analysis Set | T15_01_10_01_02_base_char_mfas |
| 16. | Table 15.1.11.1.1 | Substance Use – Safety Set | T15_01_11_01_01_substance_ss |
| 17. | Table 15.1.12.1.1 | Prior Medical History Conditions – Safety Set | T15_01_12_01_01_prior_mh_ss |
| 18. | Table 15.1.12.2.1 | Current Medical History Conditions – Safety Set | T15_01_12_02_01_current_mh_ss |
| 19. | Table 15.1.13.1.1 | Gynecological History – Safety Set | T15_01_13_01_01_gin_his_ss |
| 20. | Table 15.1.14.1.1 | VTE Risk Factors – Safety Set | T15_01_14_01_01_vte_ss |
| 21. | Table 15.1.15.1.1 | Menstrual History – Safety Set | T15_01_15_01_01_menstr_his_ss |
| 22. | Table 15.1.16.1.1 | Prior Medications, Therapies and Contraception – Safety Set | T15_01_16_01_01_prior_cm_ss |
| 23. | Table 15.1.16.2.1 | Concomitant Medications, Therapies and Contraception – Safety Set | T15_01_16_02_01_concom_cm_ss |
| 24. | Table 15.1.17.1.1 | Exposure to Investigational Medicinal Product – Safety Set | T15_01_17_01_01_exp_ss |
| 25. | Table 15.1.18.1.1 | Number of Subjects with at Least One Missing Entry of IMP Intake in Treatment Diary by Treatment Cycle and Overall – Safety Set | T15_01_18_01_01_mis_imp_ss |
| 26. | Table 15.1.19.1.1 | Number of Subjects with Gaps between Two Active Tablet Intakes of More Than 48 Hours by Treatment Cycle and Overall – Safety Set | T15_01_19_01_01_48h_gap_intake_ss |
| 27. | Table 15.1.20.1.1 | Compliance to Investigational Medicinal Product – Safety Set | T15_01_20_01_01_compl_ss |
| **Efficacy Data** | | | |
| 28. | Table 15.2.1.1.1 | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_01_01_PI_eval_less_35_C_E_mfas |

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|---|---|---|---|
| 29. | Table 15.2.1.2.1 | Overall Pearl Index in Non-Breastfeeding Women (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_02_01_PI_over_C_E_mfas |
| 30. | Table 15.2.1.2.2 | Overall Pearl Index in Non-Breastfeeding Women Aged ≤ 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_02_02_PI_over_less_35_C_E_mfas |
| 31. | Table 15.2.1.2.3 | Overall Pearl Index in Non-Breastfeeding Women Aged > 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_02_03_PI_over_more_35_C_E_mfas |
| 32. | Table 15.2.1.2.4_add | Overall Pearl Index in Non-Breastfeeding Women by BMI Subgroup (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_02_04_PI_over_BMI_C_E_mfas |
| 33. | Table 15.2.1.2.5_add | Overall Pearl Index in Non-Breastfeeding Women by BMI Subgroup (Only Confirmed Pregnancies, Including Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_02_05_PI_over_BMI_C_I_mfas |
| 34. | Table 15.2.1.2.6_add | Overall Pearl Index in Non-Breastfeeding Women by BMI Subgroup (Confirmed and Suspected, Non-confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_02_06_PI_over_BMI_CS_E_mfas |
| 35. | Table 15.2.1.2.7_add | Overall Pearl Index in Non-Breastfeeding Women by BMI Subgroup (Confirmed and Suspected, Non-confirmed Pregnancies, Including Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_02_07_PI_over_BMI_CS_I_mfas |
| 36. | Table 15.2.1.2.8_add | Overall Pearl Index in Non-Breastfeeding Women by Weight Subgroup (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_02_08_PI_over_weight_C_E_mfas |
| 37. | Table 15.2.1.2.9_add | Overall Pearl Index in Non-Breastfeeding Women by Weight Subgroup (Only Confirmed Pregnancies, Including Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_02_09_PI_over_weight_C_I_mfas |
| 38. | Table 15.2.1.2.10_add | Overall Pearl Index in Non-Breastfeeding Women by Weight Subgroup (Confirmed and Suspected, Non-confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_02_10_PI_over_weight_CS_E_mfas |
| 39. | Table 15.2.1.2.11_add | Overall Pearl Index in Non-Breastfeeding Women by Weight Subgroup (Confirmed and Suspected, Non-confirmed Pregnancies, Including Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_02_11_PI_over_weight_CS_I_mfas |
| 40. | Table 15.2.1.3.1 | Pearl Index for Method Failures in Non-Breastfeeding Women (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_03_01_PI_mf_C_E_mfas |
| 41. | Table 15.2.1.3.2 | Pearl Index for Method Failures in Non-Breastfeeding Women Aged ≤ 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_03_02_PI_mf_less_35_C_E_mfas |
| 42. | Table 15.2.1.3.3 | Pearl Index for Method Failures in Non-Breastfeeding Women Aged > 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_03_03_PI_mf_more_35_C_E_mfas |
| 43. | Table 15.2.1.4.1 | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_04_01_PI_eval_C_E_mfas |
| 44. | Table 15.2.1.4.2 | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged > 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_04_02_PI_eval_more_C_E_mfas |
| 45. | Table 15.2.1.4.3_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years | T15_02_01_04_03_PI_eval_less_35_C_I_mfas |

| | | | |
|---|---|---|---|
| | | (Only Confirmed Pregnancies, Including Sites 104 and 120) – Modified Full Analysis Set | |
| 46. | Table 15.2.1.4.4_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years (Confirmed and Suspected, Non-confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_04_04_PI_eval_less_35_CS_E_mfas |
| 47. | Table 15.2.1.4.5_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years (Confirmed and Suspected, Non-confirmed Pregnancies, Including Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_04_05_PI_eval_less_35_CS_I_mfas |
| 48. | Table 15.2.1.4.6_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years by BMI Subgroup (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_04_06_PI_eval_less_35_BMI_C_E_mfas |
| 49. | Table 15.2.1.4.7_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years by BMI Subgroup (Only Confirmed Pregnancies, Including Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_04_07_PI_eval_less_35_BMI_C_I_mfas |
| 50. | Table 15.2.1.4.8_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years by BMI Subgroup (Confirmed and Suspected, Non-confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_04_08_PI_eval_less_35_BMI_CS_E_mfas |
| 51. | Table 15.2.1.4.9_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years by BMI Subgroup (Confirmed and Suspected, Non-confirmed Pregnancies, Including Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_04_09_PI_eval_less_35_BMI_CS_I_mfas |
| 52. | Table 15.2.1.4.10_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years by Weight Subgroup (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_04_10_PI_eval_less_35_weight_C_E_mfas |
| 53. | Table 15.2.1.4.11_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years by Weight Subgroup (Only Confirmed Pregnancies, Including Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_04_11_PI_eval_less_35_weight_C_I_mfas |
| 54. | Table 15.2.1.4.12_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years by Weight Subgroup (Confirmed and Suspected, Non-confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_04_12_PI_eval_less_35_weight_CS_E_mfas |
| 55. | Table 15.2.1.4.13_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women Aged ≤ 35 Years by Weight Subgroup (Confirmed and Suspected, Non-confirmed Pregnancies, Including Sites 104 and 120) – Modified Full Analysis Set | T15_02_01_04_13_PI_eval_less_35_weight_CS_I_mfas |
| 56. | Table 15.2.2.1.1 | Overall Pregnancy Rate Life Table in Non-Breastfeeding Women (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_02_01_01_preg_rate_over_C_E_mfas |
| 57. | Table 15.2.2.1.2 | Overall Pregnancy Rate Life Table in Non-Breastfeeding Women Aged ≤ 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_02_01_02_preg_rate_over_less_35_C_E_mfas |
| 58. | Table 15.2.2.1.3 | Overall Pregnancy Rate Life Table in Non-Breastfeeding Women Aged > 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_02_01_03_preg_rate_over_more_35_C_E_mfas |

| | | | |
|---|---|---|---|
| 59. | Table 15.2.2.2.1 | Evaluable Cycles Pregnancy Rate Life Table in Non-Breastfeeding Women (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_02_02_01_preg_rate_eval_C_E_mfas |
| 60. | Table 15.2.2.2.2 | Evaluable Cycles Pregnancy Rate Life Table in Non-Breastfeeding Women Aged ≤ 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_02_02_02_preg_rate_eval_less_35_C_E_mfas |
| 61. | Table 15.2.2.2.3 | Evaluable Cycles Pregnancy Rate Life Table in Non-Breastfeeding Women Aged > 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_02_02_03_preg_rate_eval_more_35_C_E_mfas |
| 62. | Table 15.2.2.3.1 | Method Failure Life Table in Non-Breastfeeding Women (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_02_03_01_preg_rate_mf_C_E_mfas |
| 63. | Table 15.2.2.3.2 | Method Failure Life Table in Non-Breastfeeding Women Aged ≤ 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_02_03_02_preg_rate_mf_less_35_C_E_mfas |
| 64. | Table 15.2.2.3.3 | Method Failure Life Table in Non-Breastfeeding Women Aged > 35 Years (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_02_03_03_preg_rate_mf_more_35_C_E_mfas |
| 65. | Table 15.2.3.1.1_add | Overall Pearl Index in Non-Breastfeeding Women (Confirmed and Suspected, Non-confirmed Pregnancies, Including Sites 104 and 120) – Modified Full Analysis Set | T15_02_03_01_01_PI_over_CS_I_mfas |
| 66. | Table 15.2.3.1.2_add | Overall Pearl Index in Non-Breastfeeding Women (Only Confirmed Pregnancies, Including Sites 104 and 120) – Modified Full Analysis Set | T15_02_03_01_02_PI_over_C_I_mfas |
| 67. | Table 15.2.3.1.3_add | Overall Pearl Index in Non-Breastfeeding Women (Confirmed and Suspected, Non-confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | T15_02_03_01_03_PI_over_CS_E_mfas |
| **Safety Data** | | | |
| 68. | Table 15.3.1.1.1 | Summary of Adverse Events – Safety Set | T15_03_01_01_01_ae_ss |
| 69. | Table 15.3.1.1.2 | Summary of Adverse Events by Weight Subgroup – Safety Set | T15_03_01_01_02_ae_weight_ss |
| 70. | Table 15.3.1.1.3 | Summary of Adverse Events by BMI Subgroup – Safety Set | T15_03_01_01_03_ae_bmi_ss |
| 71. | Table 15.3.1.1.4 | Summary of Adverse Events by Blood Pressure Subgroup – Safety Set | T15_03_01_01_04_ae_blood_ss |
| 72. | Table 15.3.1.1.5 | Summary of Adverse Events by Race Subgroup – Safety Set | T15_03_01_01_05_ae_race_ss |
| 73. | Table 15.3.1.1.6 | Summary of Adverse Events by Ethnicity Subgroup – Safety Set | T15_03_01_01_06_ae_ethnicity_ss |
| 74. | Table 15.3.1.2.1 | Incidence of TEAEs – Safety Set | T15_03_01_02_01_teae_ SS |
| 75. | Table 15.3.1.2.2 | Incidence of TEAEs by Weight Subgroup – Safety Set | T15_03_01_02_02_teae_weight_ss |
| 76. | Table 15.3.1.2.3 | Incidence of TEAEs by BMI Subgroup – Safety Set | T15_03_01_02_03_teae_bmi_ss |
| 77. | Table 15.3.1.2.4 | Incidence of TEAEs by Blood Pressure Subgroup – Safety Set | T15_03_01_02_04_teae_blood_ss |
| 78. | Table 15.3.1.2.5 | Incidence of TEAEs by Race Subgroup – Safety Set | T15_03_01_02_05_teae_race_ss |
| 79. | Table 15.3.1.2.6 | Incidence of TEAEs by Ethnicity Subgroup – Safety Set | T15_03_01_02_06_teae_ethnicity_ss |
| 80. | Table 15.3.1.3.1 | Incidence of TEAEs by Relationship – Safety Set | T15_03_01_03_01_teae_rel_ss |
| 81. | Table 15.3.1.3.2 | Incidence of TEAEs by Relationship by Weight Subgroup – Safety Set | T15_03_01_03_02_teae_rel_weight_ss |
| 82. | Table 15.3.1.3.3 | Incidence of TEAEs by Relationship by BMI Subgroup – Safety Set | T15_03_01_03_03_teae_rel_bmi_ss |

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| 83. | Table 15.3.1.3.4 | Incidence of TEAEs by Relationship by Blood Pressure Subgroup – Safety Set | T15_03_01_03_04_teae_rel_blood_ss |
| 84. | Table 15.3.1.3.5 | Incidence of TEAEs by Relationship by Race Subgroup – Safety Set | T15_03_01_03_05_teae_rel_race_ss |
| 85. | Table 15.3.1.3.6 | Incidence of TEAEs by Relationship by Ethnicity Subgroup – Safety Set | T15_03_01_03_06_teae_rel_ethnicity_ss |
| 86. | Table 15.3.1.4.1 | Incidence of TEAEs by Worst Severity – Safety Set | T15_03_01_04_01_teae_sev_ss |
| 87. | Table 15.3.1.4.2 | Incidence of TEAEs by Worst Severity by Weight Subgroup – Safety Set | T15_03_01_04_02_teae_sev_weight_ss |
| 88. | Table 15.3.1.4.3 | Incidence of TEAEs by Worst Severity by BMI Subgroup – Safety Set | T15_03_01_04_03_teae_sev_bmi_ss |
| 89. | Table 15.3.1.4.4 | Incidence of TEAEs by Worst Severity by Blood Pressure Subgroup – Safety Set | T15_03_01_04_04_teae_sev_blood_ss |
| 90. | Table 15.3.1.4.5 | Incidence of TEAEs by Worst Severity by Race Subgroup – Safety Set | T15_03_01_04_05_teae_sev_race_ss |
| 91. | Table 15.3.1.4.6 | Incidence of TEAEs by Worst Severity by Ethnicity Subgroup – Safety Set | T15_03_01_04_06_teae_sev_ethnicity_ss |
| 92. | Table 15.3.1.5.1 | Incidence of Serious TEAEs – Safety Set | T15_03_01_05_01_saeteae_ss |
| 93. | Table 15.3.1.5.2 | Incidence of Serious TEAEs by Weight Subgroup – Safety Set | T15_03_01_05_02_saeteae_weight_ss |
| 94. | Table 15.3.1.5.3 | Incidence of Serious TEAEs by BMI Subgroup – Safety Set | T15_03_01_05_03_saeteae_bmi_ss |
| 95. | Table 15.3.1.5.4 | Incidence of Serious TEAEs by Blood Pressure Subgroup – Safety Set | T15_03_01_05_04_saeteae_blood_ss |
| 96. | Table 15.3.1.5.5 | Incidence of Serious TEAEs by Race Subgroup – Safety Set | T15_03_01_05_05_saeteae_race_ss |
| 97. | Table 15.3.1.5.6 | Incidence of Serious TEAEs by Ethnicity Subgroup – Safety Set | T15_03_01_05_06_saeteae_ethnicity_ss |
| 98. | Table 15.3.1.6.1 | Incidence of TEAEs Leading to Trial Termination – Safety Set | T15_03_01_06_01_teae_term_ss |
| 99. | Table 15.3.1.6.2 | Incidence of TEAEs Leading to Trial Termination by Weight Subgroup – Safety Set | T15_03_01_06_02_teae_term_weight_ss |
| 100. | Table 15.3.1.6.3 | Incidence of TEAEs Leading to Trial Termination by BMI Subgroup – Safety Set | T15_03_01_06_03_teae_term_bmi_ss |
| 101. | Table 15.3.1.6.4 | Incidence of TEAEs Leading to Trial Termination by Blood Pressure Subgroup – Safety Set | T15_03_01_06_04_teae_term_blood_ss |
| 102. | Table 15.3.1.6.5 | Incidence of TEAEs Leading to Trial Termination by Race Subgroup – Safety Set | T15_03_01_06_05_teae_term_race_ss |
| 103. | Table 15.3.1.6.6 | Incidence of TEAEs Leading to Trial Termination by Ethnicity Subgroup – Safety Set | T15_03_01_06_06_teae_term_ethnicity_ss |
| 104. | Table 15.3.1.7.1 | Incidence of TEAEs of Special Interest – Safety Set | T15_03_01_07_01_teae_sp_int_ss |
| 105. | Table 15.3.1.7.2 | Incidence of TEAEs of Special Interest by Weight Subgroup – Safety Set | T15_03_01_07_02_teae_sp_int_weight_ss |
| 106. | Table 15.3.1.7.3 | Incidence of TEAEs of Special Interest by BMI Subgroup – Safety Set | T15_03_01_07_03_teae_sp_int_bmi_ss |
| 107. | Table 15.3.1.7.4 | Incidence of TEAEs of Special Interest by Blood Pressure Subgroup – Safety Set | T15_03_01_07_04_teae_sp_int_blood_ss |
| 108. | Table 15.3.1.7.5 | Incidence of TEAEs of Special Interest by Race Subgroup – Safety Set | T15_03_01_07_05_teae_sp_int_race_ss |
| 109. | Table 15.3.1.7.6 | Incidence of TEAEs of Special Interest by Ethnicity Subgroup – Safety Set | T15_03_01_07_06_teae_sp_int_ethnicity_ss |
| 110. | Table 15.3.1.8.1 | Incidence of Related Serious TEAEs – Safety Set | T15_03_01_08_01_rel_saeteae_ss |
| 111. | Table 15.3.1.8.2 | Incidence of Related Serious TEAEs by Weight Subgroup – Safety Set | T15_03_01_08_02_rel_saeteae_weight_ss |
| 112. | Table 15.3.1.8.3 | Incidence of Related Serious TEAEs by BMI Subgroup – Safety Set | T15_03_01_08_03_rel_saeteae_bmi_ss |
| 113. | Table 15.3.1.8.4 | Incidence of Related Serious TEAEs by Blood Pressure Subgroup – Safety Set | T15_03_01_08_04_rel_saeteae_bood_ss |

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| 114. | Table 15.3.1.8.5 | Incidence of Related Serious TEAEs by Race Subgroup – Safety Set | T15_03_01_08_05_rel_saeteae_race_ss |
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| 116. | Table 15.3.2.1.1 | Summary of Vital Signs – Safety Set | T15_03_02_01_01_vs_ss |
| 117. | Table 15.3.2.1.2 | Summary of Vital Signs by Weight Subgroup – Safety Set | T15_03_02_01_02_vs_weight_ss |
| 118. | Table 15.3.2.1.3 | Summary of Vital Signs by BMI Subgroup – Safety Set | T15_03_02_01_03_vs_bmi_ss |
| 119. | Table 15.3.2.1.4 | Summary of Vital Signs by Blood Pressure Subgroup – Safety Set | T15_03_02_01_04_vs_blood_ss |
| 120. | Table 15.3.2.1.5 | Summary of Vital Signs by Race Subgroup – Safety Set | T15_03_02_01_05_vs_race_ss |
| 121. | Table 15.3.2.1.6 | Summary of Vital Signs by Ethnicity Subgroup – Safety Set | T15_03_02_01_06_vs_ethnicity_ss |
| 122. | Table 15.3.3.1.1 | Summary of Clinical Laboratory Tests: Hematology – Safety Set | T15_03_03_01_01_hema_ss |
| 123. | Table 15.3.3.1.2 | Summary of Clinical Laboratory Tests: Biochemistry – Safety Set | T15_03_03_01_02_bioch_ss |
| 124. | Table 15.3.3.1.3 | Summary of Clinical Laboratory Tests: Urinalysis dipstick – Safety Set | T15_03_03_01_03_urin_ss |
| 125. | Table 15.3.3.1.4 | Clinical Laboratory Tests: Incidence of Hematology Abnormalities – Safety Set | T15_03_03_01_04_hema_abn_ss |
| 126. | Table 15.3.3.1.5 | Clinical Laboratory Tests: Incidence of Biochemistry Abnormalities – Safety Set | T15_03_03_01_05_bioch_abn_ss |
| 127. | Table 15.3.3.1.6 | Clinical Laboratory Tests: Shift Table of Hematology Results – Safety Set | T15_03_03_01_06_shift_hema_ss |
| 128. | Table 15.3.3.1.7 | Clinical Laboratory Tests: Shift Table of Biochemistry Results – Safety Set | T15_03_03_01_07_shift_bioch_ss |
| 129. | Table 15.3.4.1.1 | Physical Examination – Safety Set | T15_03_04_01_01_pe_ss |
| 130. | Table 15.3.5.1.1 | Gynecological Examination – Safety Set | T15_03_05_01_01_gyn_exam_ss |
| 131. | Table 15.3.6.1.1 | Transvaginal Ultrasound Examination – Safety Set | T15_03_06_01_01_transvag_exam_ss |
| 132. | Table 15.3.6.1.2 | Shift Table for Transvaginal Ultrasound Examination – Safety Set | T15_03_06_01_02_transvag_exam_shift_ss |
| 133. | Table 15.3.7.1.1 | Dysmenorrhea Characteristic – Safety Set | T15_03_07_01_01_dysm_char_ss |
| 134. | Table 15.3.7.1.2 | Shift Table for Dysmenorrhea – Safety Set | T15_03_07_01_02_dysm_char_shift_ss |
| 135. | Table 15.3.8.1.1 | Mastodynia/Mastalgia Characteristic – Safety Set | T15_03_08_01_01_mastodyn_char_ss |
| 136. | Table 15.3.8.1.2 | Shift Table for Mastodynia/Mastalgia – Safety Set | T15_03_08_01_02_mastodyn_char_shift_ss |
| 137. | Table 15.3.9.1.1 | Summary of Cervical Cytology – Safety Set | T15_03_09_01_01_cytology_ss |
| 138. | Table 15.3.9.1.2 | Shift Table for Cervical Cytology Test – Safety Set | T15_03_09_01_02_cytology_shift_ss |
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| 139. | Table 15.4.1.1.1 | Number of Subjects with Bleeding by Treatment Day, Treatment Cycle and Reference Period – Full Analysis Set | T15_04_01_01_01_sub_bleed_day_cyc_ref_fas |
| 140. | Table 15.4.1.2.1 | Number of Subjects with Unscheduled Bleeding Days by Treatment Cycle and Reference Period – Full Analysis Set | T15_04_01_02_01_sub_ubleed_cyc_ref_fas |
| 141. | Table 15.4.1.3.1 | Number of Subjects with Scheduled Bleeding Days by Treatment Cycle and Reference Period – Full Analysis Set | T15_04_01_03_01_sub_sbleed_cyc_ref_fas |
| 142. | Table 15.4.1.4.1 | Number of Days with Bleeding by Cycle and Reference Period – Full Analysis Set | T15_04_01_04_01_day_bleed_cyc_ref_fas |
| 143. | Table 15.4.1.5.1 | Number of Days with Unscheduled Bleeding by Cycle and Reference Period – Full Analysis Set | T15_04_01_05_01_day_ubleed_cyc_ref_fas |
| 144. | Table 15.4.1.6.1 | Number of Days with Scheduled Bleeding by Cycle and Reference Period – Full Analysis Set | T15_04_01_06_01_day_sbleed_cyc_ref_fas |
| 145. | Table 15.4.2.1.1 | Number of Subjects with Spotting by Treatment Day, Treatment Cycle and Reference Period – Full Analysis Set | T15_04_02_01_01_sub_spot_day_cyc_ref_fas |

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| 146. | Table 15.4.2.2.1 | Number of Subjects with Unscheduled Spotting Days by Treatment Cycle and Reference Period – Full Analysis Set | T15_04_02_02_01_sub_uspot_cyc_ref_fas |
| 147. | Table 15.4.2.3.1 | Number of Subjects with Scheduled Spotting Days by Treatment Cycle and Reference Period – Full Analysis Set | T15_04_02_03_01_sub_sspot_cyc_ref_fas |
| 148. | Table 15.4.2.4.1 | Number of Days with Spotting by Cycle and Reference Period – Full Analysis Set | T15_04_02_04_01_day_spot_cyc_ref_fas |
| 149. | Table 15.4.2.5.1 | Number of Days with Unscheduled Spotting by Cycle and Reference Period – Full Analysis Set | T15_04_02_05_01_day_uspot_cyc_ref_fas |
| 150. | Table 15.4.2.6.1 | Number of Days with Scheduled Spotting by Cycle and Reference Period – Full Analysis Set | T15_04_02_06_01_day_sspot_cyc_ref_fas |
| 151. | Table 15.4.3.1.1 | Number of Bleeding/Spotting Episodes During Treatment and by Reference Period – Full Analysis Set | T15_04_03_01_01_epis_trt_ref_fas |
| 152. | Table 15.4.3.2.1 | Duration of Bleeding/Spotting Episodes by Cycle and Reference Period – Full Analysis Set | T15_04_03_02_01_epis_dur_cyc_ref_fas |
| 153. | Table 15.4.3.3.1 | Number of Subjects with Prolonged Bleeding/Spotting >9 and >14 by Reference Period – Full Analysis Set | T15_04_03_03_01_sub_pblsp_9_14_ref_fas |
| 154. | Table 15.4.4.1.1_add | Number of Subjects with Bleeding/Spotting by Treatment Day, Treatment Cycle and Reference Period – Full Analysis Set | T15_04_04_01_01_sub_blsp_fas |
| 155. | Table 15.4.4.2.1_add | Number of Subjects with Unscheduled Bleeding/Spotting Days by Treatment Cycle and Reference Period – Full Analysis Set | T15_04_04_02_01_sub_ublsp_fas |
| 156. | Table 15.4.4.3.1_add | Number of Subjects with Scheduled Bleeding/Spotting Days by Treatment Cycle and Reference Period – Full Analysis Set | T15_04_04_03_01_sub_sblsp_fas |
| 157. | Table 15.4.5.1.1_add | Number of Subjects with no Bleeding/Spotting Days by Treatment Cycle and Reference Period – Full Analysis Set | T15_04_05_01_01_sub_no_blsp_fas |
| 158. | Table 15.4.6.1.1_add | Number of Days with Bleeding/Spotting by Cycle and Reference Period in BMI Subgroup – Full Analysis Set | T15_04_06_01_01_days_blsp_BMI_fas |
| 159. | Table 15.4.6.2.1_add | Number of Days with Unscheduled Bleeding/Spotting by Cycle and Reference Period in BMI Subgroup – Full Analysis Set | T15_04_06_02_01_days_ublsp_BMI_fas |
| 160. | Table 15.4.6.3.1_add | Number of Days with Scheduled Bleeding/Spotting by Cycle and Reference Period in BMI Subgroup – Full Analysis Set | T15_04_06_03_01_days_sblsp_BMI_fas |
| 161. | Table 15.4.7.1.1_add | Number of Days with Bleeding/Spotting by Cycle and Reference Period in Weight Subgroup – Full Analysis Set | T15_04_07_01_01_days_blsp_weight_fas |
| 162. | Table 15.4.7.2.1_add | Number of Days with Unscheduled Bleeding/Spotting by Cycle and Reference Period in Weight Subgroup – Full Analysis Set | T15_04_07_02_01_days_ublsp_weight_fas |
| 163. | Table 15.4.7.3.1_add | Number of Days with Scheduled Bleeding/Spotting by Cycle and Reference Period in Weight Subgroup – Full Analysis Set | T15_04_07_03_01_days_sblsp_weight_fas |
| 164. | Table 15.4.7.1.1 | IMP Acceptability Assessment – Full Analysis Set | T15_04_07_01_01_imp_accept_fas |
| 165. | Table 15.4.7.2.1 | Shift table for IMP Acceptability Assessment – Full Analysis Set | T15_04_07_02_01_shift_imp_accept_fas |

## 5. Listings

Appendix tables defined below will be provided in separate .rtf files for each output.

| Seq. No | Table No and Title | | Output file name |
|---|---|---|---|
| **Demographic and Study Population Data** | | | |
| 1. | Listing 16.2.1.1 | Reasons for Exclusion from Analysis Sets – Enrolled Set | L16_02_01_01_excl_es |
| 2. | Listing 16.2.1.2 | Subject's Disposition – Safety Set | L16_02_01_02_disp_ss |

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| 3. | Listing 16.2.1.3 | Subject Visits – Enrolled Set | L16_02_01_03_visits_es |
| 4. | Listing 16.2.1.4 | Protocol Deviations Reported by Investigator – Enrolled Set | L16_02_01_04_dev_inv_es |
| 5. | Listing 16.2.1.5 | Screening Failures – Enrolled Set | L16_02_01_05_scrn_fail_es |
| 6. | Listing 16.2.1.6 | Inclusion Criteria Not Met and Exclusion Criteria Met | L16_02_01_06_incl_excl_es |
| 7. | Listing 16.2.1.7 | Demographics – Enrolled Set | L16_02_01_07_demo_es |
| 8. | Listing 16.2.1.8 | Substance Use – Enrolled Set | L16_02_01_08_subst_use_es |
| 9. | Listing 16.2.1.9 | Medical History – Enrolled Set | L16_02_01_09_mh_es |
| 10. | Listing 16.2.1.10 | Gynecological History – Enrolled Set | L16_02_01_10_gyn_his_es |
| 11. | Listing 16.2.1.11 | VTE Risk Factors – Enrolled Set | L16_02_01_11_vte_es |
| 12. | Listing 16.2.1.12 | Menstrual History – Enrolled Set | L16_02_01_12_menstr_his_es |
| 13. | Listing 16.2.1.13 | Prior and Concomitant Medications, Therapies and Contraception – Enrolled Set | L16_02_01_13_cm_es |
| 14. | Listing 16.2.1.14 | Drug Accountability – Enrolled Set | L16_02_01_14_drug_account_es |
| 15. | Listing 16.2.1.15 | Treatment Compliance According to Drug Accountability – Enrolled Set | L16_02_01_15_compl_es |
| **Efficacy Data** | | | |
| 16. | Listing 16.2.2.1 | Pregnancy Determination – Enrolled Set | L16_02_02_01_preg_determ_es |
| 17. | Listing 16.2.2.2 | Pregnancy Outcome – Enrolled Set | L16_02_02_02_preg_out_es |
| 18. | Listing 16.2.2.3 | Subjects' Decision to Become Pregnant – Enrolled Set | L16_02_02_03_decis_preg_es |
| **Safety Data** | | | |
| 19. | Listing 16.2.3.1 | Adverse Event: General – Enrolled Set | L16_02_03_01_ae_es |
| 20. | Listing 16.2.3.2 | Adverse Event: MedDRA Coding – Enrolled Set | L16_02_03_02_ae_meddra_es |
| 21. | Listing 16.2.3.3 | Serious Adverse Event – Enrolled Set | L16_02_03_03_sae_es |
| 22. | Listing 16.2.3.4 | TEAEs Leading to Trial Termination - Enrolled Set | L16_02_03_04_teae_term_es |
| 23. | Listing 16.2.3.5 | TEAEs of Special Interest – Enrolled Set | L16_02_03_05_teae_sp_int_es |
| 24. | Listing 16.2.4.1 | Vital Signs – Enrolled Set | L16_02_04_01_vs_es |
| 25. | Listing 16.2.5.1 | Laboratory Data: Hematology – Enrolled Set | L16_02_05_01_hema_es |
| 26. | Listing 16.2.5.2 | Laboratory Data: Biochemistry – Enrolled Set | L16_02_05_02_bioch_es |
| 27. | Listing 16.2.5.3 | Laboratory Data: Urinalysis – Enrolled Set | L16_02_05_03_urin_es |
| 28. | Listing 16.2.5.4 | Laboratory Data: Pregnancy Test – Enrolled Set | L16_02_05_04_preg_es |
| 29. | Listing 16.2.6.1 | Physical Examination – Enrolled Set | L16_02_06_01_pe_es |
| 30. | Listing 16.2.7.1 | Gynecological Examination – Enrolled Set | L16_02_07_01_gyn_exam_es |
| 31. | Listing 16.2.7.2 | Transvaginal Ultrasound Examination – Enrolled Set | L16_02_07_02_transv_exam_es |
| 32. | Listing 16.2.7.3 | Dysmenorrhea Characteristic – Enrolled Set | L16_02_07_03_dysm_char_es |
| 33. | Listing 16.2.7.4 | Mastodynia/Mastalgia – Enrolled Set | L16_02_07_04_mastod_char_es |
| 34. | Listing 16.2.8.1 | Cervical Cytology Results – Enrolled Set | L16_02_08_01_cytol_es |
| **Tolerability Data** | | | |
| 35. | Listing 16.2.9.1 | Treatment Diary – Full Analysis Set | L16_02_09_01_diary_fas |
| 36. | Listing 16.2.10.1 | IMP Acceptability Assessment – Full Analysis Set | L16_02_10_01_imp_accept_fas |

## 6. Figures

Appendix figures defined below will be provided in separate .rtf files for each output.

| Seq. No | Table No and Title | | Output file name |
|---|---|---|---|
| **Demographic and Study Population Data** | | | |
| 1. | Figure 15.1.1.1 | Flow Chart of Subject Disposition – Enrolled Set | F15_01_01_01_disp_es |
| 2. | Figure 15.1.2.1 | Flow Chart of Analysis Sets – Enrolled Set | F15_01_02_01_anal_es |
| **Tolerability Data** | | | |
| 3. | 15.2.1.1_add | Overall Pearl Index in Non-Breastfeeding Women by BMI and Race (Black or African-American vs White) (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | F15_02_01_01_PI_over_BMI_C_E_race_mfas |

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| 4. | Figure 15.2.1.2_add | Overall Pearl Index in Non-Breastfeeding Women by BMI and Race (Black or African-American vs White) (Only Confirmed Pregnancies, Including Sites 104 and 120) – Modified Full Analysis Set | F15_02_01_02_PI_over_BMI_C_I_race_mfas |
| 5. | Figure 15.2.1.3_add | Overall Pearl Index in Non-Breastfeeding Women by BMI and Race (Black or African-American vs White) (Confirmed and Suspected, Non-confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | F15_02_01_03_PI_over_BMI_CS_E_race_mfas |
| 6. | Figure 15.2.1.4_add | Overall Pearl Index in Non-Breastfeeding Women by BMI and Race (Black or African-American vs White) (Confirmed and Suspected, Non-confirmed Pregnancies, Including Sites 104 and 120) – Modified Full Analysis Set | F15_02_01_04_PI_over_BMI_CS_I_race_mfas |
| 7. | Figure 15.2.2.1_add | Overall Pearl Index in Non-Breastfeeding Women by BMI and Ethnicity (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | F15_02_02_01_PI_over_BMI_C_E_ethnicity_mfas |
| 8. | Figure 15.2.2.2_add | Overall Pearl Index in Non-Breastfeeding Women by BMI and Ethnicity (Only Confirmed Pregnancies, Including Sites 104 and 120) – Modified Full Analysis Set | F15_02_02_02_PI_over_BMI_C_I_ethnicity_mfas |
| 9. | Figure 15.2.2.3_add | Overall Pearl Index in Non-Breastfeeding Women by BMI and Ethnicity (Confirmed and Suspected, Non-Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | F15_02_02_03_PI_over_BMI_CS_E_ethnicity_mfas |
| 10. | Figure 15.2.2.4_add | Overall Pearl Index in Non-Breastfeeding Women by BMI and Ethnicity (Confirmed and Suspected, Non-confirmed Pregnancies, Including Sites 104 and 120) – Modified Full Analysis Set | F15_02_02_04_PI_over_BMI_CS_I_ethnicity_mfas |
| 11. | Figure 15.2.3.1_add | Pearl Index Based on Evaluable Cycles in Non-Breastfeeding Women by BMI and Race (Black or African-American vs White) (Only Confirmed Pregnancies, Excluding Sites 104 and 120) – Modified Full Analysis Set | F15_02_03_01_PI_eval_BMI_C_E_race_mfas |
| 12. | Figure 15.4.1.1 | Subjects with Bleeding by Treatment Day – Full Analysis Set | F15_04_01_01_sub_bleed_day_fas |
| 13. | Figure 15.4.1.2 | Subjects with Bleeding by Treatment Cycle – Full Analysis Set | F15_04_01_02_sub_bleed_cyc_fas |
| 14. | Figure 15.4.1.3 | Subjects with Bleeding by Reference Period – Full Analysis Set | F15_04_01_03_sub_bleed_ref_fas |
| 15. | Figure 15.4.2.1 | Subjects with Scheduled and Unscheduled Bleeding Days by Treatment Cycle – Full Analysis Set | F15_04_02_01_sub_subleed_cyc_fas |
| 16. | Figure 15.4.2.2 | Subjects with Scheduled and Unscheduled Bleeding Days by Reference Period – Full Analysis Set | F15_04_02_02_sub_subleed_ref_fas |
| 17. | Figure 15.4.4.1 | Scheduled and Unscheduled Bleeding Days by Cycle – Full Analysis Set | F15_04_04_01_subleed_day_cyc_fas |
| 18. | Figure 15.4.4.2 | Scheduled and Unscheduled Bleeding Days by Reference Period – Full Analysis Set | F15_04_04_02_subleed_day_ref_fas |
| 19. | Figure 15.4.5.1 | Subjects with Spotting by Treatment Day – Full Analysis Set | F15_04_05_01_sub_spot_day_fas |
| 20. | Figure 15.4.5.2 | Subjects with Spotting by Treatment Cycle – Full Analysis Set | F15_04_05_02_sub_spot_cyc_fas |
| 21. | Figure 15.4.5.3 | Subjects with Spotting by Reference Period – Full Analysis Set | F15_04_05_03_sub_spot_ref_fas |
| 22. | Figure 15.4.6.1 | Subjects with Scheduled and Unscheduled Spotting Days by Treatment Cycle – Full Analysis Set | F15_04_06_01_sub_suspot_cyc_fas |
| 23. | Figure 15.4.6.2 | Subjects with Scheduled and Unscheduled Spotting Days by Reference Period – Full Analysis Set | F15_04_06_02_sub_suspot_ref_fas |
| 24. | Figure 15.4.7.1 | Bleeding/Spotting Episodes by Reference Period – Full Analysis Set | F15_04_07_01_epis_ref_fas |

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|---|---|---|
| 25. | Figure 15.4.8.1 Scheduled and Unscheduled Spotting Days by Cycle – Full Analysis Set | F15_04_08_01_suspot_day_cyc_fas |
| 26. | Figure 15.4.8.2 Scheduled and Unscheduled Spotting Days by Reference Period – Full Analysis Set | F15_04_08_02_suspot_day_ref_fas |
| 27. | Figure 15.4.9.1_add Subjects with Bleeding/Spotting by Treatment Day – Full Analysis Set | F15_04_09_01_sub_blsp_day_fas |
| 28. | Figure 15.4.9.2_add Subjects with Bleeding/Spotting by Treatment Cycle – Full Analysis Set | F15_04_09_02_sub_blsp_cyc_fas |
| 29. | Figure 15.4.9.3_add Subjects with Bleeding/Spotting by Reference Period – Full Analysis Set | F15_04_09_03_sub_blsp_ref_fas |
| 30. | Figure 15.4.10.1_add Subjects with Scheduled and Unscheduled Bleeding/Spotting Days by Treatment Cycle – Full Analysis Set | F15_04_10_01_sub_sublsp_cyc_fas |
| 31. | Figure 15.4.10.2_add Subjects with Scheduled and Unscheduled Bleeding/Spotting Days by Reference Period – Full Analysis Set | F15_04_10_02_sub_sublsp_ref_fas |
| 32. | Figure 15.4.11.1_add Scheduled and Unscheduled Bleeding/Spotting Days by Cycle – Full Analysis Set | F15_04_11_01_sublsp_day_cyc_fas |
| 33. | Figure 15.4.11.2_add Scheduled and Unscheduled Bleeding/Spotting Days by Reference Period – Full Analysis Set | F15_04_11_02_sublsp_day_ref_fas |