



Sponsor: Estetra

Protocol no: MIT-Es0001-C301

Statistical Analysis Plan

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1.0 Introduction

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Estetra Protocol MIT-Es0001-C301.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol amendment 2.1 dated 6 February 2017 and CRF dated 10 April 2018. Any further changes to the protocol or CRF may necessitate updates to the SAP.

2.0 Study Objectives

2.1 Primary Objective

The primary objective of this study is to evaluate the contraceptive efficacy of 15 mg Estetrol (E4)/3 mg Drospirenone (DRSP) using the Pearl Index in subjects aged 18 to 35 years, inclusive, at the time of screening.

2.2 Secondary Efficacy Objectives

The secondary objectives of this study are:

1. To evaluate the contraceptive efficacy of 15 mg E4/3 mg DRSP using the method failure Pearl Index and life-table analysis in subjects aged 18 to 35 years, inclusive, at the time of screening
2. To evaluate the contraceptive efficacy of 15 mg E4/3 mg DRSP using the Pearl Index, the method failure Pearl Index and life-table analysis in the overall study population

2.3 Other Secondary Objectives

1. To evaluate cycle control and bleeding pattern associated with 15 mg E4/3 mg DRSP
2. To evaluate general safety of 15 mg E4/3 mg DRSP
3. To evaluate the endometrial safety using histological assessment of endometrial biopsy samples in a subset of subjects aged 18 to 50 years, inclusive, at the time of screening (endometrial safety Substudy)
4. To evaluate the impact of 15 mg E4/3 mg DRSP on physical, psychological, and social functioning and well-being

3.0 Study Design

This study is a multicenter, open-label, single-arm study.

The total duration of the study, including the screening, will range from 382 to 447 days for most of the participating subjects, which is approximately 13 months. Those subjects who discontinue and desire pregnancy will be followed for a maximum of one year after study discontinuation for return of spontaneous menstruation, until pregnancy, or until initiation of a contraceptive method (whichever occurs first).

Approximately 1550 healthy female subjects at risk for pregnancy, between 18 and 50 years old (inclusive, at the time of screening), and requesting contraception will be enrolled in the study. In total 1350 subjects will be 18 to 35 years old (inclusive). Recruitment may be stopped when 1550 subjects have been enrolled if the required number of subjects for the primary analysis (1350 subjects in the age group up to 35 years) has been reached. Recruitment in the age group > 35 years will be stopped when 200 subjects have been enrolled.

Eligible subjects will be treated with 15 mg E4/3 mg DRSP for 13 consecutive cycles. The treatment must be taken once daily at approximately the same time of the day in a 24/4-day regimen, i.e. 24 active tablets followed by 4 placebo tablets (4-day hormone free interval).

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The primary objective of the study is to evaluate the contraceptive efficacy of the new Combined Oral Contraceptive (COC), using the Pearl Index (which reflects the pregnancy rate associated with a contraceptive method) among the subjects aged 18 to 35 years inclusive.

The contraceptive efficacy will also be evaluated using the method failure Pearl Index (which reflects the pregnancy rate due to method failure only) and life-table analysis in the subjects aged 18 to 35 years inclusive and in the overall study population.

The general safety will be evaluated by the determination of routine laboratory parameters, vital signs, by performing physical, gynecological and breast examinations and by recording number, frequency, type and intensity of adverse events (AEs) and serious adverse events (SAEs).

Endometrial safety will be evaluated using histological assessments of endometrial biopsy samples.

Participating subjects will be asked to record daily in a subject diary their bleeding/spotting episodes. This will allow evaluating the bleeding pattern and the cycle control associated with the investigational product.

Treatment compliance will be assessed using data from the subject diary across the entire study and by cycle. The subject diary will also be used to determine whether or not a cycle is an at risk cycle for the Pearl Index calculation. In the primary analysis of the Pearl Index, at risk cycles will be defined as cycles in which the following criteria are met:

1. No other methods of birth control (including condoms) are used by the subject as confirmed in the subject diary
2. The subject confirmed that sexual intercourse occurred during the cycle in the subject diary

Note that if conception occurs in a cycle, then that cycle will be included as an at risk cycle in the denominator even if any other contraceptive method was used during that cycle or the subject did not confirm that sexual intercourse occurred. Cycles after the cycle of conception will not be included as at risk cycles and will be excluded from the denominator.

Physical, psychological and social functioning and well-being associated with the investigational product will be assessed with well-established questionnaires. A study schedule of events is provided in Appendix 1 of the Protocol.

3.1 Sample Size Considerations

Sample size is based on needing a sufficient number of cycles such that the difference between the Pearl Index and the upper limit of the two-sided 95% confidence interval (CI) for the Pearl Index does not exceed 1. Assuming that the true Pearl Index is 1.0 and that a Poisson model is used to derive the CIs, then at least 12,337 at risk cycles are required for a power of 90% in the 18 to 35 year old population ([Gerlinger et al., 2003](#)). Assuming a not at risk cycle rate of 10% and a dropout rate of approximately 30% (assuming an average of 4 cycles for subjects that discontinue), approximately 1350 18-to-35 year old subjects need to be enrolled. Additionally, it is planned to enroll a maximum of 200 subjects 36-50 years. Therefore, in total, approximately 1550 subjects will be enrolled in the study.

No formal sample size has been estimated for the endometrial safety sub-study.

Approximately 100 subjects with both a Screening and Visit 7a biopsies are planned to be included in the endometrial safety sub-study. Assuming a 40% dropout rate for a 13-cycle treatment will yield approximately 167 subjects who will have a screening biopsy performed at selected sites.

4.0 Study Variables and Covariates

4.1 Primary Variable

The primary efficacy variable will be the number of on-treatment pregnancies assessed by the Pearl Index in the ITT population aged 18 to 35 years, inclusive, at the time of screening with at risk cycles (cycles in

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which no other methods of birth control (including condoms) are used and during which the subjects confirmed that sexual intercourse has occurred).

4.2 Secondary Variables

4.2.1 Efficacy

The secondary efficacy variables are:

1. The number of on-treatment pregnancies as assessed by the method failure Pearl Index and the cumulative pregnancy rate in subjects aged 18 to 35 years, inclusive, at the time of screening
2. The number of on-treatment pregnancies as assessed by the Pearl Index, the method failure Pearl Index and the cumulative pregnancy rate in the overall study population

4.2.2 Other Secondary Variables

The other secondary variables are:

1. Cycle control and bleeding patterns based on vaginal bleeding information recorded daily by the subjects in the diaries
2. Safety data in the overall study population obtained from routine laboratory parameters, vital signs, and physical, gynecological and breast examinations, evaluated as the number, frequency, type and intensity of AEs and SAEs
3. Change in endometrial histology from baseline to end of treatment in subjects having been treated for at least 10 complete cycles
4. Change from baseline to end of treatment in the various items of well-established questionnaires to evaluate physical, psychological, and social functioning and well-being

4.3 Predetermined Subgroups

The key subgroup in this study is subjects aged 18 to 35 years, inclusive, at the time of screening. This subgroup is used for the primary efficacy population. All data regarding disposition, baseline characteristics, compliance, exposure and contraceptive efficacy will be presented for subjects aged 18 to 35 years and for all subjects within the specified analysis population.

In addition, subgroup analyses will be performed for the Pearl Index and vaginal bleeding data (specifically unscheduled bleeding and spotting and the absence of scheduled bleeding) for the following categories:

- Body Mass Index (BMI) categories (< 30 , ≥ 30 kg/m²) at Baseline
- Race category (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other Race)
- Starters (including true new users)/Switchers (see Section 5.5)
- Smokers/Non-smokers at Baseline
- Age (≥ 18 to ≤ 25 ; > 25 to ≤ 35 and > 35 years old) at Screening

The non-smokers group includes subjects who are former smokers and never smokers. The smokers group includes subjects who are current smokers. The other race group includes subjects who selected more than one race, or whose race was recorded as other race on the CRF.

Quality of life data will be presented for all subjects and for starters and switchers separately.

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5.0 Definitions

5.1 Cycle

The expected duration of a cycle is 28 days. A 28-day cycle consists of 24 days of active tablet intake followed by 4 days of inactive tablet intake and subjects who complete the study are expected to have completed thirteen 28-day cycles.

All cycles will be determined using the start dates recorded in the diaries. The first day of a cycle is the start date recorded on the diary for that cycle and the last day of a cycle coincides with the day before the start date recorded on the diary for the next cycle. For the last cycle (where no start date for the following cycle is available), the last day of the cycle will be assumed to be the date of last dose of study medication, whether this is an active or inactive tablet. The date of last dose of study medication in the last cycle will be derived from the data collected in the diary.

If the conception is confirmed to be during a specific cycle in the narrative and this cycle is not in the diary data, then the cycle will be included as cycle in the exposure for the derivation of the Pearl Index. If the cycle in which conception occurred is not known, cycle(s) up to the one in which the positive pregnancy occurred will be included in the exposure for the derivation of the Pearl Index.

For the analysis of bleeding data, the cycle will be shifted by 3 days with the 3 days of the next cycle included in the previous cycle. For example, in the bleeding analysis Cycle 2 will be from Day 4 of Cycle 2 to Day 3 of Cycle 3 inclusive.

The start and stop times of a cycle will be determined before determining whether the cycle is evaluable for the Pearl Index or evaluable for the bleeding data. Data review meetings may be held to determine if cycles are at risk cycles for the Pearl Index and if they are evaluable for the bleeding analysis prior to database lock (see Section 8.3) if the classification is not clear from the data collected and the rules in the SAP.

5.1.1 At Risk Cycle for Pearl Index

In the primary calculation of the Pearl Index (see Section 9.5.1 for details) and the Method failure Pearl Index, only at risk cycles will be included in the derivation of the number of women-28 day equivalent cycles of treatment, which is used as the denominator. At risk cycles will be defined as cycles in which the following criteria are both met:

1. No other methods of birth control (including condoms) are used by the subject as confirmed in the subject diary
2. The subject confirmed that sexual intercourse occurred during the cycle in the subject diary

This definition of at risk cycles will be used as the denominator for the Pearl Index for on-treatment pregnancies and also for on-treatment method failure pregnancies.

Two alternative calculations of the exposure (i.e., the denominator) will be performed to allow for comparisons with historical data:

- All exposure, which includes cycles with and without other methods of birth control and cycles with and without sexual intercourse. In this derivation of the Pearl Index **all cycles** are classed as at risk cycles with the exception of any cycles after the cycle of conception in the case of pregnancy. This denominator will be used for the Pearl Index for on-treatment pregnancies only,
- Modified at risk exposure, where only cycles with other methods of birth control are excluded, while occurrence of sexual intercourse is not taken into account. In this derivation of the Pearl Index, at risk cycles are defined as cycles in which no other methods of birth control (including condoms) are used by the subject as confirmed in the subject diary.

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Two additional alternative definitions of at risk cycles will be used for the derivation of the Pearl Index for method failure pregnancies. In the first of these definitions, cycles qualify if they meet all of the criteria 1 to 8 listed below:

1. No other methods of birth control (including condoms) are used by the subject as confirmed in the subject diary
2. The subject confirmed that sexual intercourse occurred during the cycle in the subject diary
3. A subject does not have a user failure pregnancy with an estimated conception date in that cycle or prior to that cycle and does not have a method failure pregnancy with an estimated conception date prior to that cycle
4. The subject does not receive unauthorized concomitant medication (see section 9.4.6.1 of the protocol) for at least one day during the cycle
5. The subject does not miss 4 or more days of active pills during the cycle
6. The subject does not miss 2 or more consecutive days of active pills during the cycle
7. The length of the previous cycle is not longer than 28 days
8. The subject had no adverse events of vomiting and/or diarrhea during the cycle

In the second of these definitions, cycles qualify if they meet all of the criteria 1 and 3 to 8 listed above (i.e. occurrence of sexual intercourse is not taken into account),

The following rules will be applied to all types of exposure:

- If conception occurs in a cycle, then that cycle will be included in the denominator, regardless of whether or not other methods of birth control were used during that cycle, or whether or not sexual intercourse was confirmed.
 - If the conception is confirmed to be during a specific cycle in the narrative and this cycle is not in the diary data, then the cycle will be included in the denominator, regardless of whether or not other methods of birth control were used during that cycle, or whether or not sexual intercourse was confirmed
 - The only exception is for user failure pregnancies, which will be excluded from the exposure definitions based on the compliance rules 3 to 8 above, since they do not meet criterion 3
- Cycles after the cycle of conception will be excluded from the denominator
- Missing data from the diary will be handled according to section 5.15.1.

5.1.2 Evaluable Cycle and Reference Period for Bleeding Data

Bleeding data will be analyzed by cycle and by reference period (RP). For the analysis of bleeding data by cycle, the cycle will be shifted by 3 days with the 3 days of the next cycle included in the previous cycle. For example, in the bleeding analysis Cycle 2 will be from Day 4 of Cycle 2 to Day 3 of Cycle 3 inclusive. For the 3 days after Cycle 13, the last non-missing response for bleeding in Cycle 13 will be imputed.

In determining whether a cycle is evaluable for the bleeding analysis of a specific population, the cycle based on the diary data will be used rather than the shifted cycle used to present the data.

For the ITT analysis, a cycle will be considered non-evaluable if:

- The length of the cycle is longer than 28 days.

A cycle will be considered to be non-evaluable in the per-protocol (PP) analysis for bleeding data if any of the following criteria are met:

1. A subject becomes pregnant in that cycle or prior to that cycle

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2. The length of the cycle is shorter than 22 days or longer than 28 days
3. A subject did not have a hormone-free period towards the end of the cycle (i.e. there are not at least 4 days where an active tablet was not taken between the last day an active tablet was taken in this cycle and the first day an active tablet was taken in the next cycle)
4. The subject received unauthorized concomitant medication (see section 9.4.6.1 of the protocol) thought to have the potential to impact the bleeding analysis for at least one day during the cycle
5. Use of unauthorized pre-treatment and concomitant medication thought to have the potential to impact the bleeding analysis, if cycle starts within 28 days after discontinuation of unauthorized medication
6. The subject had a positive test for chlamydia or gonorrhea during that cycle
7. The subject missed 4 or more days of active pills during the cycle
8. The subject missed 2 or more consecutive days of active pills during the cycle
9. The subject had a procedure to the vagina, cervix or endometrium during the cycle (for endometrial biopsy, please see below)
10. The subject had an endometrial biopsy taken during that cycle
 - a. If a subject had a biopsy at Screening, then any cycles that started in the 28 days after the biopsy date will be considered non-evaluable
 - b. If a subject had a post treatment biopsy during the cycle or in the 28 days prior to the start of the cycle

A cycle with missing diary bleeding data will still be considered evaluable if the criteria above are not met and bleeding data can be imputed for days with missing data (see Section 5.15.2 for details).

Three other analyses of bleeding data will be performed as follows:

1. Using cycles in which all active pills were taken as per the instructions in the protocol. In this analysis, evaluable cycles will be defined as per the PP analysis but cycles where there was at least 1 day between Day 1 and Day 24 where an active pill was not taken will be excluded.
2. Using cycles in which exactly 1 active pill was missed. In this analysis, evaluable cycles will be defined as per the ITT analysis but only cycles where there was exactly 1 missed active pill between Day 1 and Day 24 are included.
3. Using cycles in which at least 2 active pills were missed. In this analysis, evaluable cycles will be defined as per the ITT analysis but only cycles where there were at least 2 missed active pills between Day 1 and Day 24 are included.

In addition, an analysis by RP will be performed where there are 4 RPs each of 91 days in duration defined as follows:

- RP1 = Day 1 to Day 91
- RP2 = Day 92 to Day 182
- RP3 = Day 183 to Day 273
- RP4 = Day 274 to Day 364

where Day 1 is the first day of Cycle 1 reported in the subject diary and then the remaining days are fixed using Day 1 as a reference. For example, Day 91 is 90 days after the date of the first day of Cycle 1.

A RP will be considered to be non-evaluable in the ITT analysis when the RP is less than 91 days in duration (i.e. where the subject withdraws from the study during the RP). If there are any gaps between cycles in terms of date within the RP (i.e. at the end of the 4-day inactive pill period of a given cycle, the subject does

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not directly restart with the first active pill of the next pill pack), then the RP will be excluded from the ITT Population. For example, if Cycle 1 Day 28 is 1 February 2018 and Cycle 2 Day 1 is 3 February, then RP1 will be excluded from the ITT.

A RP with missing bleeding diary data will still be considered evaluable if the criteria above are not met and bleeding data can be imputed for days with missing data (see Section 5.15.2 for details).

5.2 Baseline and Change from Baseline

The Baseline value for each assessment is defined as the last measurement taken prior to first administration of study medication, unless otherwise stated. When the date of the assessment is on the date of first administration, it will be assumed that the assessment was performed prior to first dose. The Baseline value for the Menstrual Distress Questionnaire will be the value collected at Visit 3 because the date of completion is not collected in eCRF for this questionnaire.

For any parameter at a specific visit, change from Baseline is calculated as the value of that parameter at that visit minus the Baseline value of that parameter, as defined above.

5.3 On-Treatment Period

For contraceptive efficacy, the On-Treatment Period is defined as the period of time between the date of first dose of study medication and 2 days after the last dose of study medication (regardless of whether this is an active or inactive table), inclusive.

For safety (TEAEs and concomitant medication), the On-Treatment Period is defined as the period of time between the date of first dose of study medication and the date of last dose of study medication (regardless of whether this is an active or inactive table), inclusive.

If the subject had a period of time when study medication was not being taken between the date of first dose of study medication and the last dose of study medication, this time will still be considered to be during the On-Treatment Period.

5.4 Body Mass Index

BMI in kg/m² will be calculated using the following formula:

$$\text{BMI} = \frac{\text{weight}}{\text{height}^2}$$

Weight and height collected on the CRF will not be rounded prior to deriving BMI.

5.5 Switchers, Starters and True New Users

Starters are defined as subjects who have not used hormonal contraceptives within the 3 months prior to the date of first dose of study medication.

Switchers are defined as subjects who have used hormonal contraceptives within the 3 months prior to the date of first dose of study medication.

True new users are defined as subjects who have never received a hormonal contraceptive. This group of subjects is a subset of the group of subjects classed as starters.

5.6 Prior, Post-Study Treatment and Concomitant Medication Use

Medications with an end date occurring before the date of first dose of study medication will be identified as prior medications.

Medications with a start date occurring after the end of the safety On-Treatment Period will be identified as post-study treatment medications.

The following medications will be identified as concomitant medications:

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- Medications with a start date during the safety On-Treatment Period (see Section 5.3 for details)
- Medications with a start date prior to the date of first dose of study medication and an end date on or after the date of first dose of study medication

Any medications with a missing end date will be considered to be ongoing at the end of study treatment and thus would be assumed to be after the first dose of study medication and therefore assigned as a concomitant medication.

5.7 Study Treatment Compliance

Treatment compliance for the investigational product will be assessed based on the data collected in the subject diary.

5.7.1 Compliance analysis by cycle

In the compliance analysis by cycle, a cycle will only be included if there is a reported start date for that cycle. Prior to calculating any compliance data by cycle, cycles are first determined using the start date of the cycle and the start date of the next cycle, per the rules in Section 5.1. In the compliance analysis by cycle, only days within the cycle after those rules have been applied are included in the derivation of the endpoints in this Section by cycle.

The treatment compliance will be calculated as a percentage and derived for each cycle that the subject started. For each cycle, the total number of pills (active or inactive) taken will be determined from the subject diary. If an entry of the number of active (pink) or inactive (white) pills is left blank in the diary, then it will be assumed that no pills were taken on that day.

The compliance for a given cycle will be derived as

$$100 \times \frac{\text{the total number pills taken during the cycle}}{\text{the number of pills expected to be taken during the cycle}}$$

The number of pills expected to be taken during the cycle is derived as the end date of the cycle – start date of the cycle + 1 where the start and end dates of the cycles are determined using the rules in Section 5.1. In the case of early termination from the study, in the last cycle for that subject, the number of pills expected to be taken during the cycle is calculated as the date of last dose of study medication – the start date of the cycle of interest + 1.

In addition, the subject diary data will be used to identify when a pill has been missed. The number of missed pills will be derived for each cycle. In this situation, a pill is assumed to be missed if there is a day in the diary without an entry for the number of tablets or with 0 active and 0 inactive pills reported as taken. Any gaps between Day 28 of a cycle and Day 1 of the next cycle will be included as missed pills. For example, if the reported start date for Cycle 1 is 1 February and the reported start date for Cycle 2 is 3 March, then the derived end date of Cycle 1 will be 2 March and 1-2 March will be included as 2 missed pills. If there are overlapping cycles in terms of dates, then the days will be included under the latest cycle and missed pills will be reported accordingly. For example, if the subject takes pills up to Day 24 in Cycle 1, then starts Cycle 2 on the same date as Day 25 of Cycle 1, so Days 25 to Day 28 of Cycle 1 will not be included in Cycle 1 and these will not be counted as missed pills for Cycle 1.

5.7.2 Overall compliance

In the derivation of overall compliance, all data collected on days between the date of first dose and date of last dose will be included in the derivation. The overall compliance will be determined by summing the total number of pills (active or inactive) taken across all cycles. The overall compliance will be calculated as

$$100 \times \frac{\text{the total number of pills taken across all cycles}}{\text{the date of last dose – the start date of cycle 1 + 1 in days}}$$

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In the above formula, the total number of pills taken during the cycles will be the sum of pills recorded across all days between the date of first dose of study medication and the date of last dose of study medication, inclusive. For example, if there is no start date reported for Cycle 1 and there are pills reported as taken in the diary for Cycle 1, then these pills reported in Cycle 1 will not be included in the total number of pills taken as the date of first dose of study medication will be the start date reported for Cycle 2.

The total number of pills taken across all subjects will be derived by summing the number of pills taken across the study for all subjects in the Safety Population.

For drug accountability, the number of active pills dispensed will be calculated by multiplying the number of blisters dispensed by 24. The number of inactive pills dispensed will be calculated by multiplying the number of blisters dispensed by 4. The number of active and inactive pills returned will be recorded on the CRF.

5.8 Extent of Exposure

The duration of total exposure to the investigational product in days will be determined from the first and last dosing dates during the treatment period and is derived as the last dose date – the first dose date + 1. The last dose date will be the date the last tablet was taken regardless of whether this is an active or inactive tablet. The total extent of exposure across all subjects in years will be derived by summing the total exposure in days across all subjects in the Safety Population and dividing it by 365.25 to convert the units from days to years. This will be used in the derivation of event rates for adverse events as this represents the duration of the on-treatment period for treatment emergent adverse events.

The duration of actual exposure to the investigational product in days will be determined by subtracting the total number of days where no pills were taken from the duration of total exposure. The total number of days where no pills were taken is equivalent to the total number of missed pills from Section 5.7 summed across all cycles for that subject. Days where no pills were taken include days between Day 28 of a cycle and Day 1 of the next cycle where there are gaps between cycles and days within a cycle where there are no active or inactive pills taken. The total extent of actual exposure across all subjects in years will be derived by summing the exposure in days across all subjects in the Safety Population and dividing it by 365.25 to convert the units from days to years.

The duration of actual exposure will be used to determine whether or not a subject has had at least 26 weeks exposure and whether or not a subject has had at least 52 weeks exposure.

The number of cycles of treatment will be derived for each subject by determining the number of cycles as per the definition provided in Section 5.1.

5.9 Pregnancy Related Definitions

The date of conception will be estimated for each reported pregnancy by the Principal investigator. This estimated date of conception will be used to determine whether the pregnancy was pre-, on- or post-treatment. In addition, the estimated date of conception will be reviewed alongside the compliance data recorded on the subject diary and other pertinent data collected to determine whether the pregnancy is due to method or user failure. The definitions of pre-, on- and post-treatment pregnancies and for method and user failure pregnancies are provided below.

5.9.1 Pre-Treatment Pregnancies

Pre-treatment pregnancies are pregnancies with an estimated date of conception before the date of the first dose of study medication.

5.9.2 On-Treatment Pregnancies

On-treatment pregnancies are pregnancies with an estimated date of conception during the On-Treatment Period for contraceptive efficacy (see Section 5.3 for the definition of the On-Treatment Period). In cases

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where the date of conception cannot be established unequivocally (e.g. subjects is lost to follow up), this pregnancy will be considered as on-treatment pregnancy.

5.9.3 Post-Treatment Pregnancies

Post-treatment pregnancies are pregnancies with an estimated date of conception after the end of the On-Treatment Period for contraceptive efficacy.

5.9.4 Method and User Failure Pregnancies

User failure pregnancies are pregnancies where the subject did not take the study medication correctly as per Section 9.4.4 of the Protocol during the cycle in which the estimated date of conception occurred or used drugs that have the potential to trigger interactions with COC (Section 9.4.6 of the Protocol). This also applies if the subject repeatedly missed tablets during the cycle (more than 2 consecutive active pills or more than 4 active pills). Pregnancies not identified as due to user failure will be considered to be method failure pregnancies. The pregnancy narratives are used to determine whether a pregnancy is a user or method failure pregnancy.

Each on-treatment pregnancy will be reviewed in conjunction with the data collected and classified as either a method failure or a user failure pregnancy prior to database lock.

5.10 Bleeding Patterns

The subject diary data will be used to characterize bleeding patterns. Bleeding data will be analyzed by cycle and by RP.

5.10.1 Definitions of Bleeding and Spotting

Definitions for bleeding and spotting used for the cycle and RP analysis are provided in **Table 1** below. In the diary, "0" was to be ticked for no bleeding or spotting, "1" for spotting and "2" for bleeding.

Table 1: Bleeding and spotting definitions

Term	Definition
Bleeding	Evidence of vaginal blood loss that requires the use of sanitary protection with a tampon, pad or pantyliner.
Spotting	Evidence of minimal vaginal blood loss that does not require new use of sanitary protection, including pantyliners.
Bleeding day	Day where bleeding (2) was reported for that day in the subject diary
Spotting day	Day where spotting (1) was reported for that day in the subject diary
Bleeding/spotting-free day	Day where no bleeding or spotting (0) was reported in the subject diary
Bleeding/Spotting episode	One or more consecutive bleeding and/or spotting days where there are both bleeding and spotting days bounded on either end by 2 bleeding/spotting-free days
Bleeding only episode	One or more consecutive bleeding days where there are no spotting days bounded on either end by 2 bleeding/spotting-free days
Spotting only episode	One or more consecutive spotting days where there are no bleeding days bounded on either end by 2 bleeding/spotting-free days
Bleeding/spotting-free episode	Two or more consecutive bleeding/spotting-free days bounded on either end by a bleeding or spotting day

5.10.2 Cycle analysis

5.10.2.1 Definition of cycles

In the cycle analysis of a 24/4 regimen of a COC, an up to 7-day vaginal bleeding is scheduled to occur in conjunction with the first inactive tablet (Day 25) and end on Day 3 of the next cycle (expected bleeding period). In principle, no vaginal bleeding is expected to occur at other times during the cycle. This means that the remainder of the cycle constituted the expected non-bleeding period of 21 days. Therefore, any bleeding/spotting that occurs during the expected non-bleeding period (starting on Day 4 of the actual cycle up to and including Day 24) are considered as unscheduled.

The following definitions (**Table 2**) will be used for the cycle analysis:

Table 2: Bleeding/spotting definitions used for the cycle analysis

Scheduled Bleeding/Spotting (Withdrawal Bleeding/Spotting)	Any bleeding/spotting that occurs during the hormone-free interval (i.e. Days 25 – 28) and continues through Days 1-3 of the subsequent active cycle. Note: any bleeding/spotting that occurs while taking active hormones during Days 1-7 of the first cycle will be imputed as no bleeding.
Unscheduled Bleeding/Spotting	Any bleeding/spotting that occurs while taking active hormones that does not meet the criteria for scheduled bleeding/spotting.
Unscheduled Bleeding	Any bleeding that occurs while taking active hormones that does not meet the criteria for scheduled bleeding.
Unscheduled Spotting	Any spotting that occurs while taking active hormones that does not meet the criteria scheduled spotting.
Early Withdrawal Bleeding/Spotting	Any bleeding/spotting episode that starts before the scheduled bleeding/spotting period and continues into the scheduled bleeding/spotting period.
Continued withdrawal bleeding/spotting	Any bleeding/spotting episode that starts in the scheduled bleeding/spotting period and continues after the scheduled bleeding/spotting period.

Based on these definitions, the cycle analysis of bleeding/spotting episodes will perform in two ways:

- a classical approach
- a modified cycle analysis

5.10.2.2 Classical cycle analysis

In the classical analysis, early and continued withdrawal bleeding are regarded as scheduled.

The following rules will be used for the classical approach to classify each bleeding only episode, spotting only episode or bleeding/spotting episode as scheduled or unscheduled:

The episode is defined as unscheduled, if any of the following criteria are met:

- The episode has a start date after Day 7 of Cycle 1 and an end date that is on or before Day 24 of Cycle 1
- For Cycles 2 to 13, the episode has a start date after Day 3 of the cycle and an end date that is on or before Day 24 of the cycle

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The episode is defined as scheduled (withdrawal bleeding and/or spotting), if any of the following criteria are met:

- The episode has a start date after Day 24 of the cycle and an end date that is on or before Day 3 of the next cycle
- The episode has a start date after Day 24 of the cycle and an end date that is after Day 3 of the next cycle (continued withdrawal bleeding/spotting).
 - Note it is not possible to have continued withdrawal bleeding for Cycle 13 because data are not collected for Cycle 14
- The episode has a start date before Day 24 of the cycle and an end date on or after Day 25 (early withdrawal bleeding/spotting).

All bleeding days and spotting days will then be classified as scheduled or unscheduled based on whether the bleeding or spotting days are included in a scheduled or unscheduled episode using the rules in this Section above. A bleeding day or spotting day that occurs in a scheduled episode will be classified as scheduled and a bleeding day or spotting day that occurs in an unscheduled episode will be classified as unscheduled.

5.10.2.3 Modified Cycle Analysis

In the modified cycle analysis, the definitions of expected non-bleeding and expected bleeding periods are strictly followed, i.e., all bleeding episodes that overlap with expected non-bleeding intervals are considered unscheduled. Thus in this analysis, the definitions of scheduled and unscheduled bleeding/spotting episodes presented in the Table 2 are also applicable, but early and continued withdrawal bleedings are regarded as unscheduled.

Therefore, in the derivation of endpoints where early and continued withdrawal bleeding are classed as unscheduled bleeding the following rules are used to classify each bleeding only episode, spotting only episode or bleeding/spotting episode as scheduled or unscheduled:

The episode is defined as unscheduled, if any of the following criteria are met:

- The episode has a start date after Day 7 of Cycle 1 and an end date that is on or before Day 24 of Cycle 1
- For Cycles 2 to 13, the episode has a start date after Day 3 of the cycle and an end date that is on or before Day 24 of the cycle
- The episode has a start date after Day 24 of the cycle and an end date that is after Day 3 of the next cycle (continued withdrawal bleeding/spotting)
 - Note it is not possible to have continued withdrawal bleeding for Cycle 13 because data are not collected for Cycle 14
- The episode has a start date before Day 24 of the cycle and an end date that is on or after Day 25 (early withdrawal bleeding/spotting)

The episode is defined as scheduled (withdrawal bleeding and/or spotting), if the following criterion is met:

- The episode has a start date after Day 24 of the cycle and an end date that is on or before Day 3 of the next cycle

All bleeding days and spotting days will then be classified as scheduled or unscheduled based on whether the bleeding or spotting days are included in a scheduled or unscheduled episode in the same way as outlined for the classical analysis but using the rules in this Section above where early and continued withdrawal bleeding are classed as unscheduled episodes.

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5.10.3 Reference Periods (RPs)

No additional definitions other than those displayed in Table 1 were used for the reference period analysis.

5.10.4 Bleeding Endpoints for the Cycle Analysis

For the cycle analysis, the evaluable cycles will be determined as described in Section 5.1 for each subject, missing data rules are provided in Section 5.15.2 and definitions of terminology are provided in Section 5.10.1 and 5.10.2.

Depending on the approach used for the cycle analysis (the classical approach versus the modified cycle analysis), for each evaluable cycle for each subject, the following will be determined:

- Whether there was at least one unscheduled bleeding only, spotting only or bleeding/spotting episode within that cycle (see Section 5.10.2 for definition). It will be assumed that there is at least one unscheduled episode during the cycle if there is an unscheduled episode that starts in the cycle of interest
- Whether there was at least one unscheduled bleeding only episode within that cycle (see Section 5.10.2 for definition) and no unscheduled bleeding/spotting episodes and no unscheduled spotting only episodes. It will be assumed that there is at least one unscheduled bleeding only episode during the cycle if there is an unscheduled bleeding only episode that starts in the cycle of interest
- Whether there was at least one unscheduled spotting only episode within that cycle (see Section 5.10.2 for definition) and no unscheduled bleeding/spotting episodes and no unscheduled bleeding only episodes. It will be assumed that there is at least one unscheduled spotting only episode during the cycle if there is an unscheduled spotting only episode that starts in the cycle of interest
- Whether there is an absence of any bleeding or spotting (i.e. all days in the cycle are bleeding/spotting-free days)
- Whether there is an absence of scheduled bleeding only, spotting only and bleeding/spotting episodes (i.e. there is no scheduled episode with a start date during that cycle of interest)
- Whether there is early withdrawal bleeding or spotting in that cycle (i.e. there is either an early withdrawal bleeding only, spotting only or bleeding/spotting episode that starts during the cycle of interest)
- Whether there is continued withdrawal bleeding or spotting in that cycle (i.e. there is either a continued withdrawal bleeding only, spotting only or bleeding/spotting episode that starts during the cycle of interest)
- The total (scheduled + unscheduled) number of days with bleeding and/or spotting (i.e. the number of bleeding days + the number of spotting days within the bleeding only, spotting only and bleeding/spotting episodes that start during the cycle of interest)
- The total (scheduled + unscheduled) number of days with bleeding only (i.e. the number of bleeding days within the bleeding only and bleeding/spotting episodes that start during the cycle of interest)
- The total (scheduled + unscheduled) number of days with spotting only (i.e. the number of spotting days within the spotting only and bleeding/spotting episodes that start during the cycle of interest)
- The number of unscheduled days with bleeding and/or spotting (i.e. the number of bleeding days + the number of spotting days within the unscheduled bleeding only, spotting only and bleeding/spotting episodes that start during the cycle of interest)
- The number of unscheduled days with bleeding only (i.e. the number of bleeding days within the unscheduled bleeding only and bleeding/spotting episodes that start during the cycle of interest)
- The number of unscheduled days with spotting only (i.e. the number of spotting days within the unscheduled spotting only and bleeding/spotting episodes that start during the cycle of interest)

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- The number of scheduled days with bleeding and/or spotting (i.e. the number of bleeding days + the number of spotting days within the scheduled bleeding only, spotting only and bleeding/spotting episodes that start during the cycle of interest)
- The number of scheduled days with bleeding only (i.e. the number of bleeding days within the scheduled bleeding only and bleeding/spotting episodes that start during the cycle of interest)
- The number of scheduled days with spotting only (i.e. the number of spotting days within the scheduled spotting only and bleeding/spotting episodes that start during the cycle of interest)

5.10.5 Bleeding Endpoints for Analyses by RP

For the analyses by RP, the evaluable RPs will be determined as described in Section 5.1.2 for each subject, missing data rules are provided in Section 5.15.2 and definitions of terminology are provided in Section 5.10.1.

The following variables will be derived for each evaluable RP and subject:

- The total number of days with bleeding and/or spotting (i.e. the number of bleeding days + the number of spotting days within the bleeding only, spotting only and bleeding/spotting episodes that start during the RP of interest)
- The total number of days with bleeding only (i.e. the number of bleeding days within the bleeding only and bleeding/spotting episodes that start during the RP of interest)
- The total number of days with spotting only (i.e. the number of spotting days within the spotting only and bleeding/spotting episodes that start during the RP of interest)
- The number of bleeding and/or spotting episodes
- The mean duration of the bleeding and/or spotting episodes
- The number of bleeding and/or spotting free episodes
- The mean duration of the bleeding and/or spotting free episodes

For the number of bleeding and/or spotting episodes in the RP, the number of episodes is defined as the number of bleeding only episodes + the number of spotting only episodes + the number of spotting/bleeding episodes with a start date during that RP. The duration of an episode is derived as the end date of the episode – start date of the episode + 1. The mean duration of episodes in the RP is derived from the duration of all episodes with a start date during that RP. The full duration of each of the episodes is used in the derivation of the mean duration, even if the episode continues beyond the end of the RP.

5.11 Treatment-Emergent Adverse Event (TEAE)

A TEAE is defined as an AE with a start date or worsening during the On-Treatment Period for safety (see Section 5.3 for definition of the On-Treatment Period).

If the start date for an AE is missing and the end date is either missing or on or after the date of first dose of study medication, then the AE will be assumed to be treatment-emergent. However, if the start date for an AE is missing and the end date is recorded and is before the first dose of study medication, then the AE will be assumed to be non-treatment emergent.

5.12 Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF)

The total score of the Q-LES-Q-SF (see Appendix 5 of the Protocol) will be derived by summing the first 14 items to obtain the raw total score. The raw total score is then transformed into a percentage maximum using the following formula:

$$\text{Percentage Maximum} = \frac{(\text{raw total score} - 14)}{56}$$

In the case of questions with missing results, if 10 or more questions are answered, then the percentage maximum is derived as follows:

$$\text{Percentage Maximum} = \frac{(\text{raw total score for the questions answer} - \text{number of questions answer})}{(\text{the number of questions answered} \times 4)}$$

If fewer than 10 questions are answered, then the percentage maximum will be considered to be missing.

The change from Baseline at the end of treatment will be calculated for each subject.

5.13 Menstrual Distress Questionnaire

The Menstrual Distress Questionnaire (see Appendix 6 of the Protocol) will be scored according to the manual (Moos, 1968). The following scales will be derived by summing the items that fall within that specified category: pain, water retention, autonomic reactions, negative affect, impaired concentration, behavior change, arousal and control. Each of these are derived at each visit for the menstrual (most recent flow in CRF), premenstrual (4 days before in the CRF) and intermenstrual (remainder of the cycle in the CRF) phases by summing the items that fall under the specified scale. The scoring key is presented in **Table 3** below. If the subject does not answer one item on any of the scale, then the scale is calculated by deriving the mean score for the answered items and adding that number to the sum of the answered items within that scale. If 2 or more items within a scale are not answered, then the scale is missing. The change from Baseline at the end of treatment will be calculated for each subject.

Table 3: Menstrual Distress Questionnaire Scoring Key

Scale	Items
Pain	1, 2, 3, 4, 5, 6
Water Retention	7, 8, 9, 10
Autonomic Reactions	11, 12, 13, 14
Negative Affect	15, 16, 17, 18, 19, 20, 21, 22
Impaired Concentration	23, 24, 25, 26, 27, 28, 29, 30
Behaviour Change	31, 32, 33, 34, 35
Arousal	36, 37, 38, 39, 40
Control	41, 42, 43, 44, 45, 46

5.14 Return to Fertility

Each woman who discontinues the study due to a pregnancy wish will be followed-up after study treatment discontinuation to evaluate return of spontaneous menstruation, return of fertility, or initiation of hormonal contraception, whichever comes first.

The date of the first spontaneous menstruation after study discontinuation will be recorded in the eCRF and follow-up will be continued. Once a pregnancy is reported or once a new contraceptive method has been started, the date of expected pregnancy term or of contraceptive treatment initiation will be recorded in the eCRF and no further follow-up contact will be done. The time from last dose of study medication to the return to menstruation will be calculated as the date of return of menses – the date of last dose of study medication. If the subject's fertility information indicates that she had confirmation of pregnancy, then time from last dose of study medication to the estimated date of conception will be calculated as the estimated date of conception – the date of last dose of study medication. The estimated date of conception will be derived as the date of expected pregnancy term – 38 weeks (266 days). If the subject's fertility information indicates that she received a new contraceptive method, then time from last dose of study medication to

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the date of the new contraceptive method will be calculated as the date of new contraceptive method – the date of last dose of study medication.

5.15 Methods for Handling Missing Data

5.15.1 Missing Data Related to the Pearl Index and Pill Intake

In the derivation of the Pearl Index, if the subject did not respond to the question on other contraceptive methods in the subject diary, it will be assumed that another contraceptive method was used. The cycle will be classed as a not at risk cycle and excluded from the denominator of the Pearl Index. If the subject did not respond to the question on sexual intercourse in the subject diary, it will be assumed that she did not have sexual intercourse and that cycle will be classed as a not at risk cycle and excluded from the denominator of the Pearl Index as appropriate.

For compliance, if the number of active (pink) and inactive (white) pills is blank in the diary, then it will be assumed that no pills were taken on that day.

If there is a partial start date for a cycle, then the start date will be imputed as the day after the date of Day 28 of the previous cycle, providing the imputed date is consistent with the non-missing part of the date reported and that the duration of the cycle is consequently consistent with the expected 28 days.

5.15.2 Missing Bleeding Data

One or two consecutive days with missing bleeding information will be interpolated with the bleeding information from the previous day. For three or more consecutive days with missing bleeding information, missing data will be interpolated using the worst bleeding observation of the bordering days. If there are 3 or more consecutive days with missing bleeding information at the end of the diary with no non-missing data reported afterwards, then the missing bleeding information will be interpolated with the bleeding information from the day immediately prior to the missing days. Data missing after withdrawal from the study will not be imputed.

In the case of an ambiguous response for bleeding on a given day, the worst response recorded will be used. For example, if both bleeding and spotting are reported, then the response will be set to bleeding. If both bleeding and absence of vaginal bleeding or spotting are reported, then the response will be set to bleeding. If both spotting and absence of vaginal bleeding or spotting are reported, then the response will be set to spotting. If bleeding, spotting and absence of vaginal bleeding or spotting are reported, then the response will be set to bleeding.

The first 7 days of Cycle 1 will be imputed with no bleeding. It will be assumed that the bleeding data for the 3 days after the end of Cycle 13 is the same as that of the last day of Cycle 13 where bleeding data were recorded.

5.15.3 Missing or Partial Dates for Medications

In the determination of whether a medication is taken during the On-Treatment Period, the following rules for missing and partial dates will be applied:

- If the end date is before the first dose of study medication, then the medication is a prior medication, regardless of whether or not the start date is missing or partially missing
- If the end date is on or after the date of first dose of study medication, then the following rules will be applied for missing or partially missing start dates:
 - If the start date is completely missing, then the medication will be assumed to be concomitant.
 - If only the year of the start date is recorded and the year is either before or the same year as the end of the safety On-Treatment Period, then the medication will be assumed to be concomitant.

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- If only the year of the start date is recorded and the year is after the year of the end of the safety On-Treatment Period, it will be considered to be a post-study treatment medication.
- If only the year and the month of the start date is recorded and the month specified is either before or the same month as the end of the safety On-Treatment Period, then the medication will be assumed to be concomitant
- If only the year and the month of the start date is recorded and the month specified is after the month of the end of the safety On-Treatment Period, it will be considered to be a post-study treatment medication.

5.15.4 Missing or Partial Dates for AEs

If the start date for an AE is missing and the end date is either missing or on or after the date of first dose of study medication, then the AE will be assumed to be treatment-emergent. However, if the start date for an AE is missing and the end date is recorded and is before the first dose of study medication, then the AE will be assumed to be non-treatment emergent.

6.0 Analysis Sets

6.1 Screened Population

The Screened Population includes all subjects who signed an informed consent (IC) form.

The Screened Population will be used for disposition data and data will be displayed for subjects aged 18 to 35 years and for all subjects in separate columns.

6.2 Enrolled Population

The Enrolled Population includes all enrolled subjects (i.e. subjects who had a non-missing enrollment date on the enrollment page of the CRF).

The Enrolled Population will be used for summaries of enrollment per country.

6.3 Safety Population

The Safety Population includes all enrolled subjects who receive at least one dose of study medication.

If a subject returns all study medication that was dispensed, then the subject will not be included in the Safety Population. If there is at least one pill that was dispensed but was not returned, but the subject diary has no pills recorded as taken, then it will be assumed that the subject has not taken any study medication and will not be included in the Safety Population. In the case of missing diary data, it will be assumed that no pills were taken for the corresponding days with missing data. If there was at least one pill that was dispensed but was not returned and the subject has taken at least one pill according the subject diary, then that subject will be included in the Safety Population.

The Safety Population will be used for compliance and exposure data with data displayed for subjects aged 18 to 35 years and for all subjects in separate columns. The Safety Population will also be used for safety presented for all subjects.

Follow-up evaluations will be presented for subjects in the Safety Population who discontinued study medication with pregnancy wish as the reason for discontinuation.

6.4 Intention-to-Treat (ITT) Population

The ITT Population includes all enrolled subjects who receive at least one dose of study medication. The ITT Population is the same as the Safety Population for this study.

The ITT Population will be used for baseline and contraceptive efficacy data with data displayed for subjects aged 18 to 35 years and for all subjects in separate columns. The ITT Population will also be used for

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protocol deviations, bleeding, endometrial substudy and quality of life data with data presented for all subjects.

Endometrial biopsy data will be presented for subjects in the ITT Population who had signed the informed consent form for the endometrial biopsy Substudy. Only subjects who had 2 biopsies will be included in the summary tables for the endometrial biopsy data. Subjects who are pregnant at the time that the biopsies were taken will be excluded from the summary tables.

6.5 Per-Protocol (PP) Population

The bleeding data cycle analysis will be presented in the PP Population. For the bleeding analysis, the PP Population will exclude cycles based on the rules in Section 5.1.2. Subjects in the ITT Population with at least one evaluable cycle for the bleeding analysis will be included in the PP Population and only their evaluable cycles will be included in the PP analysis for bleeding data. Subjects will be excluded from the PP Population entirely if they have no evaluable cycles for the bleeding analysis.

7.0 Interim Analyses

There are no planned interim analyses for this study.

8.0 Data Review

8.1 Data Handling and Transfer

Processes for data handling and transfer will be documented in the Data Management Plan.

8.2 Data Screening

Beyond the data screening built into the PRA Data Management Plan, the PRA programming of analysis datasets, tables, figures, and listings (TFL) provides additional data screening. Presumed data issues will be output into SAS logs identified by the word "Problem" and extracted from the logs by a SAS macro and sent to Data Management.

Review of a pre-freeze TFL run on clean subjects and a post-freeze TFL run on the frozen database allow for further data screening prior to lock. The post-freeze TFL will be discussed with the sponsor in a data review meeting to identify any final data issues and seek corrections prior to database lock. The PRA statistician and the sponsor must approve database lock.

8.3 Data Review Meetings

Data review meetings will be held during the course of the study prior to database lock and the following may be reviewed during these meetings:

- Important protocol deviations and exclusion from the PP Population
- Classification of at risk and not at risk cycles for the Pearl Index derivation where the classification is not clear based on the data collected and the rules in the SAP
- Classification of on-, pre- and post- treatment pregnancies for the Pearl Index derivation
- Classification of method failure and user failure pregnancies for the method failure Pearl Index derivation
- Classification of evaluable and non-evaluable cycles for the PP bleeding analysis where the classification is not clear based on the data collected and the rules in the SAP

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9.0 Statistical Methods

All analyses will be conducted using SAS version 9.4 or higher.

No formal statistical analyses will be performed in this study.

The following conventions will be used when presenting summary statistics for study data:

- Continuous variables will be summarized using the following descriptive statistics: number of subjects (n), mean, standard deviation (SD), standard error of the mean (SEM), median, minimum (min), maximum (max), 25th percentile (lower quartile or Q1) and 75th percentile (upper quartile or Q3)
- Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category. For AE tables, m may also be presented which represents the number of events. Percentages will be presented to 1 decimal place
- The number of subjects or observations will be presented as an integer
- Mean, median, lower quartile and upper quartile will be presented to 1 decimal place more than the raw value
- Min and max will be presented to the same number of decimal places as the raw value
- Standard deviation will be presented to 2 decimal places more than the raw value, up to a reasonable number of decimal places (i.e., rarely more than 3 decimal places unless the nature of the data suggests this)
- The denominator for percentage calculations will be the number of non-missing observations at that visit. Where this isn't appropriate, the number of subjects in the relevant population will be used

9.1 Subject Disposition

All summaries in this Section will be presented for subjects aged 18 to 35 years and for all subjects. This will be based on the Screened Population.

The number and percentage of subjects treated in the study will be presented, together with the number and percentage of subjects who completed the study and the number and percentage of subjects who withdrew from the study prematurely with a breakdown of the corresponding reasons for withdrawal. If a subject returns all study medication that was dispensed, then the subject will not be classed as treated. If there is at least one pill that was dispensed but was not returned, but the subject diary has no pills recorded as taken, then it will be assumed that the subject has not taken any study medication and will not be classed as treated. In the case of missing diary data, it will be assumed that no pills were taken for the corresponding days with missing data. If there was at least one pill that was dispensed but was not returned and the subject has taken at least one pill according the subject diary, then that subject will be classed as treated.

Tabulations of the number and percentage of subjects included in each analysis set will be provided. The percentage will not be presented for the Screened and Enrolled Populations. Percentages will be derived based on the number of subjects enrolled.

A tabulation of the number and percentage of subjects enrolled at each site and country will be summarized in the Enrolled Population.

Disposition data and the site and country will be listed in the Enrolled Population. Information on inclusion in each of the analysis sets will be listed in the Screened Population. Screening failures will be listed with the reason for the screening failure.

The cumulative discontinuation rate, as determined by life-table methods, together with the corresponding 95% CIs will be presented in the ITT population for all subjects and for subject's aged 18 to 35 years inclusive at Screening. The life-table analysis will evaluate the cumulative probability of discontinuation from the study by cycle using PROC LIFETEST in SAS where the time variable is the cycle where the

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discontinuation occurred for subjects who discontinued from the study prematurely. Subjects who did not discontinue from the study prematurely will be censored in Cycle 13. The rate of discontinuation and 95% CIs will be calculated based on Kaplan-Meier estimates for each cycle. Additionally, the estimated survival function against time (cycle) will be provided.

9.2 Protocol Deviations and Violations

The important protocol deviations for this study will be specified in the Protocol Deviation Guidance Template. Per PRA processes, protocol deviations will be entered into PRA's Clinical Trials Management System (CTMS). The study team and the sponsor will conduct ongoing reviews of the protocol deviations from CTMS to identify deviations which meet the criteria for important.

The number and percentage of subjects who had an important protocol deviation will be summarized in the ITT Population.

All important protocol deviations will be listed in the ITT Population.

The important protocol deviations will be reviewed and their potential to impact the analysis of the bleeding data will be assessed against the rules specified in Sections 5.1.2. If there is a potential for a specific important protocol deviation to impact this analysis, then the impacted cycles for that subject will be excluded from the PP analysis for bleeding data. Subjects with no evaluable cycles will be excluded from the PP Population for the analysis of bleeding data. The PP Population and the cycles to be excluded from the PP analysis must be finalized at the post-freeze data review meeting (or earlier), prior to database lock.

9.3 Treatments

All summaries described in this Section will be presented for subjects aged 18 to 35 years and for all subjects in the Safety Population.

9.3.1 Extent of Study Drug Exposure

The overall duration of total exposure and actual exposure will be summarized using descriptive statistics. In addition, the total extent of exposure and total extent of actual exposure across all subjects will be summarized in years.

Additionally, the number and percentage of subjects exposed for at least 26 weeks and at least 52 weeks based on actual exposure will be presented. The denominators for calculating the percentages will be based on the number of subjects.

The number of cycles as defined in Section 5.1 will also be summarized using descriptive statistics. The number and percentage of subjects who had at least 1, 2, 3, etc. cycles will be summarized.

Exposure data will be listed for all subjects in the Safety Population.

9.3.2 Treatment Compliance

Treatment compliance by cycle and overall will be summarized using descriptive statistics including the following information:

- The number of pills taken
- The compliance

The number and percentage of subjects missing no pills, 1 pill, 2 pills and more than 2 pills will be summarized for each cycle where the cycle is defined as per Section 5.1. The denominator will be the number of subjects in the Safety Population who started that cycle.

The total number of pills taken across all subjects will be presented. Compliance data will be listed for all subjects in the Safety Population. Drug accountability data will be listed only in the Safety Population.

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9.3.3 Prior, Post-Study Treatment and Concomitant Medications

Medications received prior to or concomitantly with study drug, categorized by preferred term according to WHODRUG Mar 2016 will be summarized in the Safety Population. The number and percentage of subjects using each medication will be displayed. This will be repeated for prior medications.

All prior, post-study treatment and concomitant medications will be listed in the Safety Population.

9.4 Demographic and Baseline Characteristics

All summaries described in this Section will be presented for subjects aged 18 to 35 years and for all subjects.

The following demographic data and baseline characteristics will be summarized in the ITT and PP Populations:

- Age at Screening
- Age group (≥ 18 to ≤ 25 years, >25 to ≤ 35 years, >35 to ≤ 50 years) at Screening
- Highest education level
- Ethnicity
- Race
- Height
- Weight at Baseline
- BMI at Baseline
- BMI categories ($<30\text{kg/m}^2$, $\geq 30\text{kg/m}^2$) at Baseline

If subjects record more than one race, then for the summary table, these subjects will be included in the Other Race group. BMI will be derived programmatically from the height and weight collected.

The subject's previous contraceptive method used will be summarized in terms of the number and percentage of switchers, starters and true new users in the ITT Population. Note: subjects who are true new users are a subset of the starters.

The following information will be summarized for gynecological history in the ITT Population:

- Gravidity and parity status
- Menstrual cycle length for starters
- Dysmenorrhea
- Previous contraceptive method used
- History of pregnancy during accurate hormonal contraceptive use

Smoking status, including the following information for current smokers will be presented in the ITT Population:

- The number of days per week where the subject smokes
- The number of tobacco products per day that the subject smokes

All demographic data, baseline characteristics, gynecological history, contraceptive use and smoking status will be listed in the ITT Population. In the demography listing, if a subject has more than one race recorded, then all races selected will be listed for that subject.

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Medical history will be summarized in the ITT. Medical history will be classified into a standardized terminology using the Medical Dictionary for Regulatory Activities (MedDRA) system organ classifications and preferred terms. Version 19.0 of MedDRA will be used as coding dictionary.

Surgical history will not be summarized.

All medical and surgical history recorded will be listed in the ITT Population.

9.5 Efficacy Analyses

9.5.1 Primary Variable

The primary variable will be summarized using the Pearl Index in the ITT population aged 18 to 35 years inclusive at Screening with at risk cycles. Subjects in this age group will not be censored on their 36th birthday for the pregnancy assessment. The Pearl Index will be presented with corresponding 95% CIs. No formal statistical analyses will be conducted for the primary variable.

The Pearl Index, defined as the number of pregnancies per 100 women-years of treatment, will be calculated as

$$\text{Pearl Index} = \frac{1300 \times \text{number of on-treatment pregnancies}}{\text{number of women} - 28 \text{ day equivalent cycles of treatment}}$$

Only at risk cycles will be included in the denominator of the Pearl Index calculation. At risk cycles will be defined as cycles in which the following criteria are met:

1. No other methods of birth control (including condoms) are used by the subject as confirmed in the subject diary
2. The subject confirmed that sexual intercourse occurred during the cycle in the subject diary

Note that if conception occurs in a cycle, then that cycle will be included as an at risk cycle in the denominator even if other methods of birth control were used during that cycle or the subject did not confirm that they had had sexual intercourse. Cycles after the cycle of conception will not be included as at risk cycles and will be excluded from the denominator.

The number of women-28 day equivalent cycles of treatment is the sum of the number of at risk cycles across all subjects. The total number of at risk cycles will be presented in the table.

All on-treatment pregnancies will be included in the numerator for the Pearl Index (see Section 5.9.1 for definition of on-treatment pregnancies).

For calculation purposes a cycle will be defined as per Section 5.1.1.

The 95% CI for Pearl Indices will be calculated using a Poisson distribution. The confidence interval limits are calculated by the following equations:

$$CI_{LOWER} = 1300 \times \frac{\frac{1}{2} \chi_{0.025; 2x}^2}{\text{the number of women} - 28 \text{ day equivalent cycles of treatment}}$$

$$CI_{UPPER} = 1300 \times \frac{\frac{1}{2} \chi_{0.975; 2(x+1)}^2}{\text{the number of women} - 28 \text{ day equivalent cycles of treatment}}$$

where x is the number of on-treatment pregnancies.

The Pearl Index and corresponding 95% CIs will be presented by the subgroups described in Section 4.3 for subjects aged 18 to 35 years. All subject diary data, pregnancy information and at risk cycles for each analysis will be listed.

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9.5.2 Secondary Variables

9.5.2.1 Pearl Index

The Pearl Index and corresponding 95% CIs will be presented for all subjects in the ITT Population (see Section 9.5.1 for details) including only at risk cycles in the denominator. At risk cycles will be defined as cycles in which no other methods of birth control (including condoms) are used by the subject as confirmed in the subject diary, and the subject confirmed that sexual intercourse occurred during the cycle in the subject diary. The number of on-treatment pregnancies and at risk cycles will be presented.

The Pearl Index and corresponding 95% CIs will be presented for subjects aged 18 to 35 years and for all subjects in the ITT Population including all cycles in the denominator with the exception of cycles after the cycle of conception in the case of pregnancy.

The Pearl Index and corresponding 95% CIs will also be presented for subjects aged 18 to 35 years and for all subjects in the ITT Population employing a modified at risk definition. With this definition, at risk cycles will be defined as cycles in which no other methods of birth control (including condoms) are used by the subject while cycles with and without confirmed intercourse are being included in the denominator.

9.5.2.2 Method Failure Pearl Index

The method failure Pearl Index is calculated using the same method as the Pearl Index (see Section 9.5.1 for details), but includes only those pregnancies that were classified as method failure (see Section 5.9.4 for details). Pregnancies due to user failure will be excluded from the numerator.

The method failure Pearl Index and corresponding 95% CIs will be presented for subjects aged 18 to 35 years at Screening in the ITT Population and for all subjects in the ITT Population including only at risk cycles in the denominator. The number of on-treatment pregnancies and at risk cycles will be presented.

This will be derived in 4 ways:

- Including all at risk cycles in the denominator where at risk cycles will be defined as cycles in which no other methods of birth control (including condoms) are used by the subject as confirmed in the subject diary and the subject confirmed that sexual intercourse occurred during the cycle in the subject diary.
- Including all at risk cycles in the denominator employing a modified at risk definition. With this definition, at risk cycles will be defined as cycles in which no other methods of birth control (including condoms) are used by the subject while cycles with and without confirmed intercourse are being included in the denominator.
- Including only at risk cycles in the denominator where at risk cycles will be defined as cycles in which no other methods of birth control (including condoms) are used by the subject as confirmed in the subject diary and the subject confirmed that sexual intercourse occurred during the cycle in the subject diary where the subject was compliant with the dosing rules 3 to 8 in Section 5.1.1.
- Including only modified at risk cycles in the denominator where at risk cycles will be defined as cycles in which no other methods of birth control (including condoms) are used by the subject as confirmed in the subject diary where the subject was compliant with the dosing rules 3 to 8 in Section 5.1.1 while cycles with and without confirmed intercourse are being included in the denominator.

9.5.2.3 Life-Table Rates

In addition, the cumulative pregnancy rate, as determined by life-table methods, together with the corresponding 95% CIs will be presented for all pregnancies and for all method failure pregnancies in the ITT population for all subjects and for subject's aged 18 to 35 years inclusive at Screening.

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Life-table analyses will provide one-year life-table pregnancy rates for each efficacy endpoint (i.e. for all pregnancies as used in the Pearl Index and for all method failure pregnancies as used in the method failure Pearl Index). The life-table analysis will evaluate the cumulative probability of pregnancy by cycle using PROC LIFETEST in SAS where the time variable is the cycle where the estimated conception occurred for subjects who had an on-treatment event of pregnancy. Subjects who did not have an on-treatment event of pregnancy will be censored on the cycle prior to the cycle in which they discontinued from the study. The rate of pregnancy and 95% CIs will be calculated based on Kaplan-Meier estimates for each cycle. Additionally, the estimated survival function against time (cycle) will be provided.

9.5.3 Bleeding and Spotting

Bleeding patterns will be analyzed using data from the subject diary. A cycle analysis and an analysis by RP will be performed (see Section 5.1.2 for details). Derived data for bleeding and spotting will be listed in the ITT Population.

9.5.3.1 Cycle Analysis

The cycle analysis will be performed following two approaches: a classical (for details see Section 5.10.2.2) and a modified cycle analysis (for details see Section 5.10.2.3).

The classical analysis will be performed in the ITT and PP Population. This analysis will also be repeated for the following populations:

- The PP analysis excluding cycles where there is at least 1 day where an active pill was missed
- The ITT analysis including only cycles where 1 active pill was missed
- The ITT analysis including only cycles where 2 or more active pills were missed.

The number of subjects with evaluable cycles for each population will be summarized by cycle.

The modified cycle analysis where early and continued withdrawal bleeding are classed as unscheduled bleeding will be performed in the ITT Population, PP Population and the PP Population excluding cycles where there is at least 1 day where an active pill was missed.

Details of the exclusion of cycles from the PP Population are provided in Section 5.1.2. Vaginal bleeding will be classified as spotting or bleeding and scheduled or unscheduled based on the definitions in Section 5.10.1 and 5.10.2. Rules for handling missing data are provided in Section 5.15.2. The inclusion of cycles in ITT Population, PP Population and PP Population excluding cycles with at least 1 active pill missed in the cycle will be listed by subject and cycle along with reasons for exclusion of the cycle from the PP Population analysis and the number of missed pills.

The following information will be summarized for bleeding and spotting for the **cycle analysis**:

- Number and percentage of subjects with unscheduled bleeding and/or spotting episodes for each cycle (classical analysis + modified cycle analysis)
- Number and percentage of subjects with unscheduled bleeding only episodes for each cycle (classical analysis + modified cycle analysis)
- Number and percentage of subjects with unscheduled spotting only episodes for each cycle (classical analysis + modified cycle analysis)
- Number and percentage of subjects with absence of a scheduled bleeding and/or spotting episode for each cycle (classical analysis + modified cycle analysis)
- Number and percentage of subjects with early withdrawal bleeding and/or spotting for each cycle
- Number and percentage of subjects with continued withdrawal bleeding and/or spotting for each cycle

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- Number and percentage of subjects with absence of any bleeding and/or spotting for each cycle
- Descriptive statistics (e.g., mean, SD, median, minimum, and maximum) for the number of days of bleeding and/or spotting, bleeding only, and spotting only within a cycle for (classical and modified cycle analysis):
 - Total Days (Unscheduled + Scheduled)
 - Unscheduled Days
 - Scheduled Days
- Cumulative number and percentage of subjects with amenorrhea in the ITT Population only (classical and modified analysis)
 - The number of subjects who have no scheduled bleeding and/or spotting episode that started in at least 1 cycle, at least 2 cycles, at least 3 cycles and so on up to at least 13 cycles. The denominator is the number of subjects with at least 1 evaluable cycle, at least 2 evaluable cycles, at least 3 evaluable cycles and so on up to at least 13 evaluable cycles, respectively, for the specified population

Note that the denominator for the percentages listed above will be the number of subjects with an evaluable cycle unless otherwise specified.

The percentage of subjects with bleeding, the percentage of subjects with spotting and the percentage of subjects with absence of bleeding and/or spotting for each day will be presented in a bar chart over time for the ITT, PP Populations and Populations based on active pill counts. The denominator will be the number of subjects with an evaluable cycle for the specified population on that day.

The descriptive statistics (e.g., mean, SD, median, minimum, and maximum) for the number of unscheduled bleeding and/or spotting days, bleeding days, and spotting days within a cycle will also be summarized in subjects who experienced an unscheduled bleeding and/or spotting episode within that cycle. This will be presented for the classical and modified analysis in the ITT and PP Populations. Additionally, unscheduled bleeding and spotting and the absence of scheduled bleeding will be summarized for all subgroups specified in Section 4.3 by cycle for the classic cycle analysis for the ITT, PP Population and the PP Population excluding cycles with at least 1 missed active pill and the modified cycle analysis for the ITT Population.

9.5.3.2 Reference Period Analysis

All RP analysis will be performed in the ITT Population only. The following information will be summarized for bleeding and spotting for the **RP analysis**:

- Descriptive statistics (e.g., mean, SD, median, minimum, and maximum) for the number of days of bleeding and/or spotting, bleeding only, and spotting only within a RP.
- Descriptive statistics for the number of bleeding and/or spotting episodes in each RP
- Descriptive statistics for the mean duration of the bleeding and/or spotting episodes in each RP
- Descriptive statistics for the number of bleeding and/or spotting free episodes in each RP
- Descriptive statistics for the mean duration of the bleeding and/or spotting free episodes in each RP

Note that the denominator for the percentages listed above will be the number of subjects with an evaluable RP.

The number of subjects with evaluable reference periods for each population will be summarized by reference period. The inclusion of reference periods in ITT Population will be listed by subject and reference period along with reasons for exclusion of the reference period.

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9.6 Safety Analyses

9.6.1 Adverse Events

TEAEs will be classified into a standardized terminology using the MedDRA system organ classifications and preferred terms. Version 19.0 of MedDRA will be used as coding dictionary. The incidence of TEAEs will be summarized for the Safety Population.

A summary of TEAEs including the number of events reported, the annual rate and the number and percentage of subjects reporting the following will be presented:

- Any TEAE
- Any TEAE leading to death
- Any treatment-emergent SAE
- Any TEAE leading to premature discontinuation from the study
- Any SAE related to study medication

TEAEs are defined in Section 5.11. The annual rate will be derived as the number of events divided by the total exposure across all subjects in years.

A breakdown of the number and percentage of subjects reporting each TEAE with the corresponding number of events, categorized by body system and preferred term coded according to the MedDRA dictionary, will be presented. Note that subjects are only counted once within each body system or preferred term but subjects with multiple events of a specific type will be counted once for each occurrence in the number of events column.

A further tabulation of these data, categorized by relationship to study drug, will be presented. Subjects with multiple events within a particular body system or preferred term will be counted under the category of their most drug-related event within that body system or preferred term in column for the number of subjects. In the column for the number of events, multiple events of a specific type and relationship will be counted once for each occurrence. Relationship to study drug is categorized as not related (not related and unlikely on the CRF) and related (possible, probable and highly probable on the CRF). This will be repeated for TEAEs leading to premature discontinuation from the study.

TEAEs will also be presented by severity. For each system organ class and preferred term, subjects are included only once, at the maximum severity. In the column for the number of events, multiple events of a specific type and severity will be counted once for each occurrence.

All adverse events (including non-treatment-emergent events) recorded on the CRF will be listed. The following listings will be generated in the Screened Population:

- All AEs
- AEs leading to premature discontinuation from the study

9.6.2 Deaths and Serious Adverse Events

A tabulation of SAEs, categorized by relationship to study drug, will be presented. Subjects with multiple events within a particular body system or preferred term will be counted under the category of their most drug-related event within that body system or preferred term in column for the number of subjects. In the column for the number of events, multiple events of a specific type and relationship will be counted once for each occurrence. Relationship to study drug is categorized as not related (not related and unlikely on the CRF) and related (possible, probable and highly probable on the CRF).

The following listings will be generated including non-treatment emergent events in the Screened Population:

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- All SAEs
- All AEs leading to death
- All SAEs related to treatment (includes SAEs where the relationship to study drug is possible, probable and highly probable)

9.6.3 Laboratory Data

Central laboratory data will be used for the tables and listings. The scheduled laboratory assessments will be included in the tables where data are available. If a specific parameter is missing at the scheduled assessment and there is an unscheduled assessment collected at the same visit where this parameter is not missing, then the value at the unscheduled assessment will be used in the table. Otherwise unscheduled assessments will not be included in the tables. Note that unscheduled pregnancy tests will be used in the assessment of pregnancies for the primary endpoint. The parameters listed in **Table 4** will be summarized. Separate outputs will be provided for hematology, serum chemistry and lipid profile.

Table 4: Laboratory Parameters

Hematology	
Hemoglobin	Mean cell volume
Hematocrit	White blood cell & Differential
Red blood cell count	Platelet count
Serum Chemistry	
Albumin	Total protein
Alanine aminotransferase (ALAT)	Serum creatinine
Aspartate aminotransferase (ASAT)	Sodium
Blood urea nitrogen	Potassium
Gamma glutamyl transferase (GGT)	Calcium
Glucose	Chloride
Glycated hemoglobin	Bicarbonate
Lactate dehydrogenase (LDH) 1 and LDH 2	Phosphorus
Total bilirubin	Choriogonadotropin Beta (Serum Pregnancy Test)
Estimated Glomerular Filtration Rate (eGFR)	
Lipid Profile	
Total cholesterol	Triglycerides
High density lipoprotein cholesterol	Low density lipoprotein cholesterol

For continuous clinical laboratory analytes, the absolute value and change from baseline will be summarized by analyte and visit using descriptive statistics for the Safety Population.

Shifts to values outside of the normal range will be presented by analyte and visit and will be summarized by the number and percentage of subjects with evaluable shifts. The denominators for calculating the percentages will be the number of subjects in the Safety Population with both the Baseline value and the value at the specified visit recorded.

If the value is below the lower limit of quantification, then half the lower limit of quantification will be used in the summary tables to calculate the descriptive statistics. If the value is above the upper limit of quantification, then the upper limit of quantification will be used in the summary tables to calculate the descriptive statistics. In the listings, values will be listed as collected without the imputation applied.

All clinical laboratory values, abnormal clinical laboratory values, and clinical significant laboratory values will also be provided in data listings in the Safety Population including data collected at any unscheduled assessments.

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Chlamydia and gonorrhea test results will be listed.

9.6.4 Vital Signs

Unscheduled vital signs assessments will be excluded from the tables.

Vital sign measurements (systolic blood pressure, diastolic blood pressure and heart rate) for the Safety Population will be summarized using descriptive statistics by visit. The change from Baseline will also be summarized in the same manner.

Weight and BMI measurements for the Safety Population will be summarized using descriptive statistics by visit. The change from Baseline will also be summarized in the same manner. BMI will be derived programmatically from the height and weight collected.

All vital signs, weight and BMI measurements will be listed in the Safety Population including data collected at any unscheduled assessments.

9.6.5 Physical and Gynecological Examinations

Physical and gynecological examination assessments will be summarized for the Safety population by visit. For each body system and assessment category, the number and percentage of subjects will be presented. The denominators for calculating the percentages will be based on the number of subjects evaluated for a particular body system. Unscheduled physical examinations will not be summarized.

All physical and gynecological examination data will be listed in the Safety Population.

9.7 Other Secondary Endpoints

9.7.1 Quality of Life

Quality of life data will be summarized in the ITT Population. Summaries will be provided overall and by switchers and starters separately.

For the Q-LES-Q-SF, the absolute values and change from baseline of the percentage maximum, how satisfied have you been with your medication and how would you rate your overall life satisfaction and contentment during the past week will be summarized descriptively by visit.

For the Menstrual Distress Questionnaire, the absolute values and change from baseline for the scores for pain, water retention, autonomic reactions, negative affect, impaired concentration, behaviour change, arousal and control will be summarized descriptively by visit and by phase. The phases are menstrual (most recent flow), premenstrual (four days before) and intermenstrual (remainder of cycle).

All quality of life data will be listed in the ITT Population.

9.7.2 Follow-Up Evaluations

The number and percentage of subjects who had pregnancy confirmation, return to menses and received a new contraceptive method after discontinuation of study treatment will be summarized. The denominator used for the percentages will be the number of subjects in the Safety Population who discontinued study medication due to a pregnancy wish.

The time from last dose of study medication to return of menses will be summarized using descriptive statistics in the Safety Population.

The following will be summarized using descriptive statistics for subjects in the Safety Population who discontinued study medication due to a pregnancy wish who selected the corresponding fertility information:

- Time from last dose of study medication to estimated date of conception
- Time from last dose of study medication to new contraceptive method

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The estimated date of conception is derived as the expected date of pregnancy term – 38 weeks (266 days).

Data for follow-up evaluations will be listed for subjects in the Safety Population who discontinued study medication due to a pregnancy wish.

9.7.3 Endometrial Biopsy Data

Only subjects in the ITT Population who had signed the informed consent form for the endometrial biopsy Substudy and who had 2 biopsies (one at Screening and one at Visit 7a) will be included in the summary tables for the endometrial biopsy data. Subjects who are pregnant at the time that the biopsies were taken will be excluded from the summary tables. The number and percentage of subjects in each histological category will be presented at the Screening Visit (Visit 1) and at Visit 7a for subjects who have completed at least 10 cycles. In addition, a shift table will be presented from the Screening Visit to Visit 7a with the number of subjects with evaluable histological data at Screening Visit and at Visit 7a the denominator.

All endometrial biopsy data will be listed.

10.0 Validation

PRA's goal is to ensure that each TFL delivery is submitted to the highest level of quality. PRA's quality control procedures will be documented separately in the study specific Quality Control Plan.

11.0 References

Gerlinger, C., Endrikat, J., van der Meulen, E. A., Dieben, T. O. & Dusterberg, B. Recommendation for confidence interval and sample size calculation for the Pearl Index. *Eur.J.Contracept.Reprod.Health Care* 8, 87-92 (2003).

Moos, R. H. The development of a menstrual distress questionnaire. *Psychosom Med* 30, 853-867 (1968).

12.0 Amendment to the Statistical Analysis Plan

12.1 Amendment 1 from SAP dated 15 July 2016

The key changes to the SAP in amendment 1 are as follows:

- Missing data rules moved to one section for missing data
- The addition of analyses for the Pearl Index to look at the rate of on-treatment pregnancies and on-treatment method failure pregnancies where the at risk cycles are defined as cycles in which no other methods of birth control are used by the subject
- The addition of an analysis for the Pearl Index to look at the rate of method failure on-treatment pregnancies excluding at risk cycles that were not compliant according to Section 9.4.4 of the protocol
- Clarification of the definition of the evaluable cycles for the bleeding analysis in the PP Population in cases where the post Screening biopsy was not performed during Cycle 13
- Addition of criteria for exclusion from the PP Population to exclude cycles within 28 days after prohibited mediations
- Clarification that the Baseline value for the Menstrual Distress Questionnaire is the value collected at Visit 3 as the date of collection is not collected
- Clarification added that compliance by cycle will be based on the cycles defined from the start dates of the cycles per Section 5.1 including detail on how gaps between cycles and overlapping cycles are handled
- Clarification added that for overall compliance only pills reported between the start and stop date for study medication will be included in the numerator
- The addition of actual exposure accounting for days where no pills were taken

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- Addition of the number of subjects with bleeding only episodes and spotting only episodes by cycle as endpoints
- Change in the definitions of unscheduled and scheduled bleeding and spotting days to use the episodes
- Clarification added for imputation for missing bleeding data to cover scenarios where 3 or more days having missing data at the end of the diary data collected
- The definition of an evaluable reference period was updated to exclude reference periods where there are gaps between the cycles
- Cumulative amenorrhea rate added as an endpoint
- Bleeding analysis section restructured and split out into the classical cycle analysis (including early and continued withdrawal bleeding as scheduled) which is now classed as the primary definition and the modified analysis (including early and continued withdrawal bleeding as unscheduled) which is no longer classed as the primary definition
- Analyses of bleeding data added for cycles with exactly 1 missed active pill and for cycles with at least 2 missed active pills
- The bleeding analysis by reference period was simplified to no longer differentiate between scheduled and unscheduled bleeding
- Clarification on the scales derived for the Menstrual Distress Questionnaire added
- Enrolled Population definition corrected to use the enrollment date
- PP Population corrected to make it clear that only the PP Population for bleeding is being derived
- Reference to ATC classification removed as data are not coded to ATC in this study
- Clarification added to indicate that BMI will be programmatically derived from height and weight for the vital signs and demography tables
- Listing added for the at risk cycles for each Pearl Index analysis
- Clarification added to categorize relationship to study medication as not related and related for AEs
- Change to the handling of unscheduled laboratory assessments and clarification added for values above the upper limit of quantification and values below the lower limit of quantification
- Choriogonadotropin beta and eGFR added as laboratory parameters to be summarized
- Addition of summaries and listings of evaluable cycles and reference periods for the bleeding analysis
- Clarification added that subjects who are pregnant at the time that the endometrial biopsies were performed will be excluded from summary tables for endometrial biopsies and the analysis set for endometrial biopsy data changed from the Safety Population to the Full Analysis Set
- Bleeding and spotting analysis section moved to Section 9.5

12.2 Amendment 2 from Amendment 1 dated 19 April 2018

The key changes to the SAP in amendment 2 are as follows:

- Correction to the definition of the alternative definition of at risk cycles that will be used for the derivation of the Pearl Index for method failure pregnancies based on compliance to indicate that all 8 criteria need to be met for a cycle to be at risk
- Correction to definition of the presence of a bleeding only unscheduled episode and the presence of a spotting only unscheduled episode for the cycle analysis for bleeding
- Addition of a section for missing or partial dates for AEs
- Addition of a new analysis of the method failure Pearl Index including only modified at risk cycles in the denominator where at risk cycles will be defined as cycles in which no other methods of birth control (including condoms) are used by the subject as confirmed in the subject diary where the subject was compliant with the dosing rules 3 to 8 in Section 5.1.1 while cycles with and without confirmed intercourse are being included in the denominator

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- Clarification added on how to handle pregnancies for the at risk cycles when the cycle is not in the diary data
- Clarification added on the handling of partial dates in the diary data
- Addition of summary tables of unscheduled bleeding and spotting days in subjects who had unscheduled bleeding and/or spotting episodes
- Clarification added that the exclusion of cycles for unauthorized medications may be different between the bleeding analysis and contraceptive efficacy

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Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse Event
ALAT	Alanine Aminotransferase
ASAT	Aspartate Aminotransferase
BMI	Body Mass Index
CI	Confidence Interval
COC	Combined Oral Contraceptives
CRF	Case Report Form
CTMS	Clinical Trials Management System
DRSP	Drospirenone
E4/3	Estetrol
eGFR	estimated Glomerular Filtration Rate
GGT	Gamma Glutamyl Transferase
IC	Informed Consent
ITT	Intention-to-Treat
LDH	Lactate dehydrogenase
LOCF	Last Observation Carried Forward
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum
n	Number of subjects
PP	Per Protocol
Q1	25 th percentile or lower quartile
Q3	75 th percentile or upper quartile
Q-LE5-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire Short Form
RP	Reference Period
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SEM	Standard Error of the Mean
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, Figures and Listings