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A Phase 3, Multicenter, Open-Label, Single Arm Study of MR-100A-01 in Women of Childbearing Potential to Evaluate Contraceptive Efficacy and Safety

Statistical Analysis Plan

[redacted]

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Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with [redacted] and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

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REVISION HISTORY

[redacted]

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LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
ADaM	Analysis Data Model
ADaM IG	Analysis Data Model Implementation Guide
AE	Adverse event
AS	Adhesion Score
ATC	Anatomical Therapeutic Chemical Level
BMI	Body Mass Index
BP	Blood Pressure
BPM	Beats per Minute
BUC	Back-up contraception
ß-hCG	Beta-Human Chorionic Gonadotropin
CEP	Contraceptive efficacy population
CI	Confidence interval
CL	Confidence Limit
COVID-19	Corona Virus Disease 2019
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
DMC	Data Monitoring Committee
DSMB	Data and Safety Monitoring Board
DTMS	Data Transfer Mapping Specification
e-CRF	Electronic case report form
EDC	Estimated Date of Conception
e-Diary	Electronic Diary
EE	Efficacy Evaluable
EOS	End-of-Study
ET	Early termination
HIV	Human Immunodeficiency Virus

Abbreviation / Acronym	Definition / Expansion
HLGT	High-Level Group Term
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MF	Method Failure
MM	Medical Monitor
N/A	Not Applicable
NCS	Not Clinically Significant
PCS	Potentially Clinically Significant
PD	Protocol Deviation
PI	Pearl Index
PK	Pharmacokinetics
PRC	Pregnancy Review Committee
PT	Preferred Term
PR	Pulse Rate
RR	Respiratory Rate
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SDTM IG	Study Data Tabulation Model Implementation Guide
SI	Sexual Intercourse
SOC	System Organ Class
SPT	Serum Pregnancy Test
TDS	Transdermal System
TEAE	Treatment-emergent adverse event

Abbreviation / Acronym	Definition / Expansion
TEMA	Treatment-emergent markedly abnormal
TLFs	Tables, Listings and Figures
UPT	Urine Pregnancy Test
VTE	Venous thromboembolism
WHO	World Health Organization

1 INTRODUCTION

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs). It describes the variables, populations, anticipated data transformations and other details of the analyses not provided in the Clinical Study Protocol.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, [redacted]
- Electronic Case Report Form (e-CRF), [redacted]
- Electronic Diary (e-Diary) Project Requirements Specification, [redacted]

The SAP describes the statistical analysis as it is planned in the protocol. If circumstances should arise during the study rendering this analysis inappropriate, or if in the meantime improved methods of analysis should arise, updates to the analysis may be made. Any protocol amendment or significant change between the planned analysis and this SAP that occurs prior to database lock will be addressed in an SAP amendment.

Post-database lock modifications (defined as changes and/or additions to the analyses planned in the final SAP) will be documented in a Statistical Analysis Modification Request form.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To determine the contraceptive efficacy of MR-100A-01 when used over 13 cycles [of 4 weeks (28-day)] in healthy, post-menarcheal, premenopausal, heterosexually active female subjects of childbearing potential who are at least 16 years of age and at risk of pregnancy.

2.2 Secondary Objective

- To determine the overall safety and tolerability profile of MR-100A-01 in terms of incidence of adverse events, cycle control, and patch adhesion.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This phase 3 study is designed as a multicenter, open-label, single-arm study in healthy, post-menarcheal, premenopausal, heterosexually active women of childbearing potential of at least 16 years of age, who are at risk of pregnancy and are seeking hormonal contraception for at least 12 months (13 cycles).

An adequate number of subjects will be screened so that approximately 1,200 women meeting all study criteria will be enrolled. [redacted] At least 200 subjects will complete the study.

There will be a screening period of 7 to 60 days and a treatment period of approximately 12 months (13 cycles).

Enrolled subjects will use MR-100A-01 patches for up to 13 cycles. The treatment regimen is a 4-week treatment cycle, with one MR-100A-01 patch to be applied every 7 days for 3 consecutive weeks followed by 1 week of a patch-free period; in the event of patch detachment or delayed patch application, the 4-week treatment cycle may be shortened.

Table 3-1 Patch Application Schedule

Week	**Cycles 1 – 13**		**Patch Application Schedule**
Week 1	Day 1	Patch on	New patch should be applied
Week 2	Day 8	Patch change	Previous patch should be removed, and a new patch should be applied
Week 3	Day 15	Patch change	Previous patch should be removed, and a new patch should be applied
Week 4	Day 22	Patch removal	Previous patch should be removed (Days 22-28 will be patch-free)

Qualifying subjects with a negative urine pregnancy test (UPT) result and having a minimum of 70% screening e-Diary compliance will be enrolled into the study.

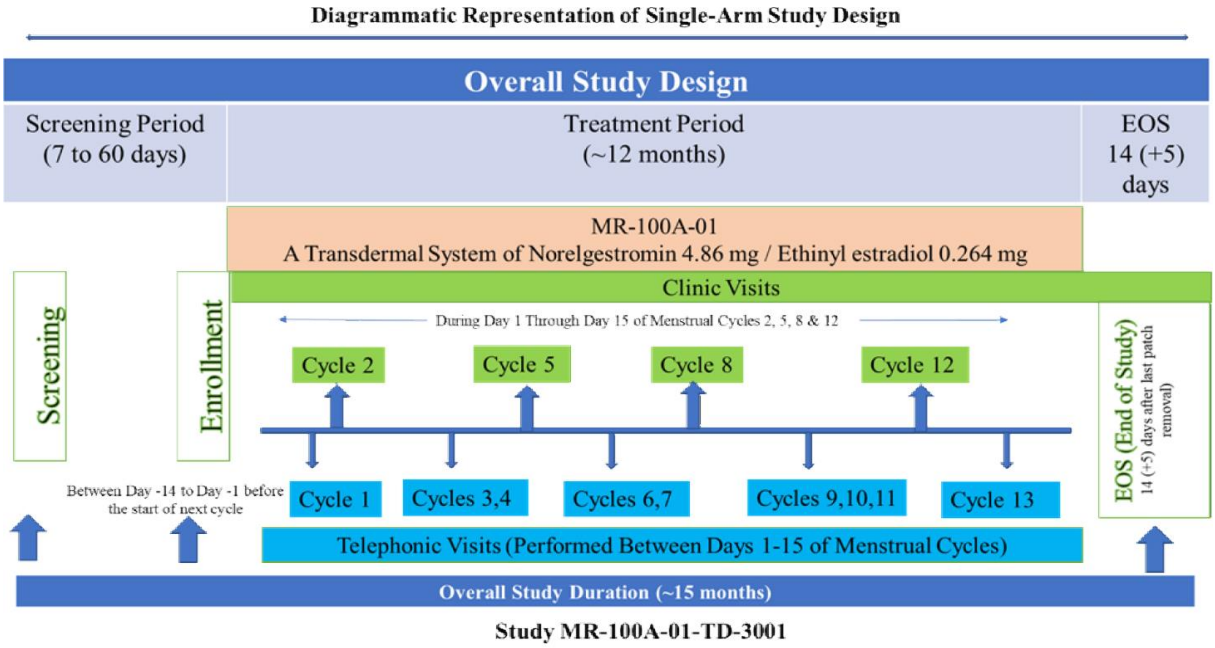
All pregnancies with an estimated date of conception (EDC) between the date of the first patch application of the study and 7 days (inclusive) of the removal of the last patch of the study will be considered as 'on-treatment' pregnancies. EDC will be separately estimated by the investigator, medical monitor (MM) and an independent Pregnancy Review Committee (PRC). MM and the PRC will classify each pregnancy as pre-treatment, on-treatment, or post-treatment based on pre-specified definitions. The latest EDC assessment by investigator will be used to determine which cycle the on-treatment pregnancy happened in for the purpose of the analyses. If the EDC as assessed by the investigator happens after the calculated last day of the last cycle the pregnancy will be attributed to the last cycle of treatment for such a subject.

The investigator/designee will evaluate the treatment compliance by reviewing the e-Diary. The subject should be considered for discontinuation due to non-compliance if the risk of pregnancy is related to non-compliance. Subjects with 2 consecutive cycles with no sexual activity or with 2 consecutive cycles with use of back-up contraception, will be considered as non-compliance related to sexual activity. Similarly, the subjects with repeated failure to enter e-Diary data related to assessments of study drug compliance, sexual activity, and use of back up contraception will be considered as non-compliance related to e-Diary entry. The investigator should discuss the specific circumstances leading to these events with the subject and medical monitor.

The End-of-Study (EOS) Visit will be performed 14 (+5) days after the end of treatment (i.e., day of removal of the last patch in the study).

Below is the study diagram (*Figure 1)*:

Figure 1: Study Diagram



3.2 Endpoints

Primary Endpoint

The primary efficacy endpoint will be pregnancy rate described by Pearl Index (PI).
PI is defined as the number of pregnancies per 100 women-years and will be calculated as follows:

$$\text{Pearl Index} = \frac{number\ of\ on{-}treatment\ pregnancies \times 13}{number\ of\ evalable\ cycles} \times 100$$

where,

- On-treatment pregnancy is defined as a pregnancy with an estimated date of conception between the date of application of the first patch through 7 days after removal of the last patch in the study.
- Evaluable cycles are defined as the complete or incomplete 28-day cycles in which vaginal intercourse occurred and in which no back-up contraception was used based on the electronic diary (e-Diary) data unless a pregnancy occurred in such a cycle.

Reported cycles after the cycle in which a pregnancy started according to the investigator will not be considered evaluable.
Cycles beyond Cycle 13 will not be considered evaluable.

Secondary Endpoints

Secondary Efficacy Endpoints:

1. Cycle-wise and cumulative pregnancy rates over 1 year evaluated using life table analysis
2. Method failure PI

Secondary Safety Endpoints:

a. Adverse Events and Tolerability:

1. Incidence of adverse events (AEs) and serious adverse events (SAEs)
2. Incidence of application site reactions

b. Cycle Control and Patch Adhesion:

1. Number of episodes and days of scheduled and unscheduled bleeding
2. Proportion of subjects reporting scheduled and unscheduled bleeding
3. Adhesion performance as measured by adhesion scores (AS)

3.2.1 Efficacy Variables

Primary variable:

Contraceptive efficacy will be evaluated by calculation of pregnancy rates using the PI.

Secondary variables:

Cycle-wise and gross cumulative probability of pregnancy will also be measured using a life table analysis. All pregnancies with an EDC between the date of the first patch application of the study and 7 days (inclusive) of the removal of the last patch of the study will be considered as 'on-treatment' pregnancies.

3.2.2 Safety Variables

The following safety variables will be collected as mentioned in the protocol study schedule, *Table 6-1*:

- Targeted physical examinations and gynecological examination
- Vital signs (sitting blood pressure [BP] and pulse rate (PR), body temperature, respiratory rate (RR))
- Clinical laboratory tests (hematology, serum chemistry, Serum Pregnancy Test (SPT), chlamydia and gonorrhea screening, Human Immunodeficiency Virus (HIV) testing, cervical cancer screening and urine drug screen parameters)
- Adverse event (AE) assessments (laboratory tests or physical examinations, evaluation of Venous thromboembolism (VTEs))
- Cycle control evaluation (bleeding and/or spotting episodes, scheduled and unscheduled bleeding/spotting)
- Assessment of patch adhesion (self-reported and investigator/sub-investigator assessed)
- Assessment of local tolerability such as skin irritation (self-reported and investigator/sub-investigator assessed)
- Concomitant medication assessments

3.2.3 Exploratory Variables

Not applicable

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures, and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard [redacted] procedures.

4.2 General Presentation Considerations

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum, and number of observations, unless otherwise stated. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using 'N' as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only. Percentage will be presented as whole number if count is 100.

If for any summary table, n is less than three then only n, minimum, and maximum should be presented, and other summary statistics will be left blank.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Pearl indices, cumulative pregnancy rates and their confidence intervals (CIs) will be presented with 2 decimal places.

Records from prior screenings for re-screened subjects will not be included in the analyses unless specified otherwise in the analysis.

In the by visit tables and figures, only the scheduled visits will be presented. In the by visit listings all visits will be presented.

Generally, for the analyses based on the CRF data the CRF reported cycles will be used. Generally, for the analyses based on the e-Dairy data the e-Diary reported cycles will be used.

Cycles beyond Cycle 13 will be included in the overall summaries and listings, unless otherwise specified, however, they will not be presented explicitly in the by cycle summaries, unless otherwise specified.

4.3 Analysis and Data Conventions

Data summaries will include the sample size, mean, median, standard deviation, minimum, and maximum for continuous variables and the number and percentage of subjects for each outcome for categorical variables. All statistical analyses will be performed using SAS®, Version 9.4 or later if available at [redacted]

4.3.1 Multi-center Studies

Data from all participating centers will be pooled prior to analysis. Summaries of demographic data, treatment compliance data and primary efficacy variable data will be provided.

4.3.2 Adjustments for Covariates

Not applicable.

4.3.3 Handling of Dropouts or Missing Data

4.3.3.1 Missing Data Related to the Pearl Index

In the derivation of the Pearl Index (PI), if the subject had sexual intercourse but 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 classified as a not evaluable cycle and excluded from the denominator of the PI.

If the subject did not respond to any question on sexual intercourse for a cycle in the subject diary, it will be assumed that she did not have sexual intercourse and that cycle will be classified as a not evaluable cycle and excluded from the denominator of the PI as appropriate.

In a cycle, if the subject has provided response at least once to the question on sexual intercourse but has missed to respond for the remaining period, it will be assumed that there was no sexual intercourse for the missing period. The cycle classification as evaluable or non-evaluable will be based on the available responses for that cycle.

[redacted]

4.3.3.2 Missing Bleeding Pattern

Only one missing day of bleeding/spotting information will be imputed: if either both bordering records have bleeding/spotting or both bordering records have no bleeding/spotting reported. All other missing cases will remain missing. If both bordering records are spotting records the imputed day will be a spotting day, otherwise, if both or at least one of the bordering records is a bleeding record, the missing day will be a bleeding day. If both bordering records are non-bleeding/spotting records the missing record will be a non-bleeding/spotting record.

Only non-missing data after imputation will be reported in the bleeding/spotting analyses with the following exception: if the subject had only bleeding/spotting and no missing information, days of no bleeding will be 0. And vice versa, if the subject only had non-bleeding days and no missing data, bleeding/spotting will be 0.

The first 7 days of Cycle 1 will be imputed with no bleeding unless the subject was enrolled under scenario 1, not current users of hormonal contraception. It will be assumed that the bleeding data for the 4 days after the end of the last cycle is the same as that of the last day of the last cycle where bleeding data were recorded.

If the information about sanitary protection is missing it will be assumed that sanitary protection was used.

4.3.3.3 Missing Dates for AEs/ Medications

If the start date for an AE is missing and the end date is either missing or on or after the date of first patch application, 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 study patch application, then the AE will be assumed to be non-treatment emergent.

Otherwise, the AE will be assigned to pre-therapy or post-therapy, depending on when the AE began.

While complete start and end dates are expected for the AEs, if there are partial dates, they will be compared to the first patch application date or the date of the last day of the subject's final treatment cycle based on the part of the partial date that is not missing. If the non-missing part of the partial date is the same as the respective part of the first patch application date or the date of the last day of the subject's final treatment cycle the AE will be considered treatment emergent.

All AEs are expected to have an end date unless they are ongoing at the end of the study. If an end date is missing or unknown, then ongoing will be assumed.

No imputation of missing AE attributes (e.g., unknown severity) besides causality will be performed.

In the determination of whether a medication is taken during the on-treatment period, the following rules for missing dates will be applied:

- If the end date is before the first patch application, then the medication is a prior medication, regardless of missing start date.
- If the end date is on or after the date of first patch application and the start date is completely missing, then the medication will be assumed to be both prior and concomitant.

Otherwise, the medication will be assigned to prior, prior and concomitant or concomitant based on the medication start and end dates.

While complete start and end dates are expected for the medications, if there are partial dates, they will be compared to the first patch application date or the last patch wearing date based on the part of the partial date that is not missing. If the non-missing part of the partial date is the same as the respective part of the first patch application date or the last patch wearing date the medication will be considered concomitant.

4.3.3.4 Missing Dates for Start and Stop of Treatment

If the subject has no diary data but has a pregnancy that is classified as on-treatment or post treatment, then the subject will be classed as treated. The treatment start date and treatment stop date would be unknown in this situation.

If the subject has no diary data but indicated they wore a patch in EDC the treatment start date will be imputed with the date of enrollment.

Where the information about whether the patch was worn on a specific day is missing, this day will be imputed as a patch wearing day if there is evidence the same patch was worn in later days: if in the next non-missing day the subject answered they wore a patch and did not report a patch change, if in the next non-missing day the subject indicated they removed a patch or if the subject indicated they replaced the next patch on time.

If the subject responded they did not apply a new patch or responded they did not remove a patch to a respective prompt it will be assumed that they continued wearing the patch they were wearing on the previous day. The same will be assumed about the date of data entry for the days when the subject entered a retrospective patch application into the e-Diary. If the previous day was not a patch wearing day the patch wearing will not be extended for the records described earlier in this paragraph.

However, if the start and stop dates for patch application remain missing then compliance and exposure will not be calculated. Similarly, the cycle of discontinuation of patch application cannot be determined and therefore this would remain missing for such subjects.

4.3.3.5 Missing Data Related to Patch Adhesion Score, Skin Irritation Score and Patch Water Exposure Score

Subjects will self-report patch adhesion score and water exposure score in their e-Diary on all days except during the patch-free week. Subjects will self-report skin irritation score in their e-Diary on all days.

Adhesion, irritation and water exposure will not be imputed. Adhesion and water exposure records after the last day the last patch was worn in a cycle will not be analyzed. Such irritation records will only be considered for the maximum score per cycle but not for the maximum scores per patch. Adhesion and irritation scores from the records when the patch was changed or removed will be attributed to the previous patch.

The worst score will be used as the score for a patch or a cycle, disregarding the missing scores. If there were no scores in a patch or a cycle reported by a subject, a missing category will be displayed in the tables.

The maximum subject-reported patch adhesion, skin irritation and patch water exposure scores will be reported in the summaries for individual cycles and for all cycles combined.

Investigator will perform evaluation of patch adhesion and skin irritation during the clinic visits. If the clinic visit happens during a patch free week, the investigator assessment should be missing.

4.3.4 Handing of Data Issues

[redacted]

4.3.5 Multiple Comparisons/Multiplicity

This study has only one primary variable, hence, no adjustments for multiplicity are required.

4.3.6 Interim Analyses

No statistical interim analysis is planned for this study.

4.3.7 Examination of Subgroups

Subgroup analyses will be performed based on baseline BMI, body weight, age, race, ethnicity, and previous hormonal contraceptive use as for the EE population:

1. BMI and weight:
    - Normal: BMI < 25 kg/m^2 and overweight: BMI ≥25 to <30 kg/m^2
    - Weight categories defined by median and/or quartiles
2. Age (<18, ≥18 years to ≤35 years at enrollment)
3. Race (White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian and Other Pacific Islander)
4. Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
5. Previous hormonal contraceptive use status:
    - Naïve Users: women who have not previously used any hormonal contraceptive
    - Prior Users: women with previous use of hormonal contraceptives but not in the 6 months prior to enrollment
    - Recent Users: women who are not currently using a hormonal contraceptive, but have used a hormonal contraceptive within 6 months prior to enrollment
    - Current Users: women who are currently using a hormonal contraceptive
6. Previous contraceptive use status:
    - Naïve Users: women who have not previously used any contraceptive
    - Prior Users: women with previous use of contraceptives but not in the 6 months prior to enrollment
    - Recent Users: women who are not currently using a contraceptive, but have used a contraceptive within 6 months prior to enrollment
    - Current Users: women who are currently using a contraceptive
7. Previous hormonal patch contraceptive use status:
    - Naïve Users: women who have not previously used any hormonal patch contraceptive
    - Prior Users: women with previous use of hormonal patch contraceptives but not in the 6 months prior to enrollment
    - Recent Users: women who are not currently using a hormonal patch contraceptive, but have used a hormonal patch contraceptive within 6 months prior to enrollment
    - Current Users: women who are currently using a hormonal patch contraceptive

Summaries of the primary efficacy variable by subgroup will be produced. The Pearl Index and corresponding 95% CIs will also be presented by subgroups. No formal statistical analysis will be performed within subgroup.

4.4 Definitions

4.4.1 Baseline

'Baseline' is defined as the last available assessment prior to the first study patch application.

'At enrollment' is equivalent to 'at baseline".

4.4.2 Study days

Study days will be calculated relative to the day of first study patch application. The first day of patch application will be Day 1 and the day prior to the first patch application will be Day -1. The last day of patch exposure will be the date when the last patch is removed or the last date the patch is reported as being worn, based on the e-Diary, wherever possible. Instructions for delayed/missed patch applications or patch changes and for patch removal are described in Section 5.1.4 of the protocol.

4.4.3 Cycle

The expected duration of a cycle is 28 days, with one MR-100A-01 patch to be applied every 7 days for 3 consecutive weeks followed by 1 week of a patch-free period.

All cycles will be determined using the start dates recorded in the e-Diaries.

The first day of a cycle is the date of first patch application recorded in the e-Diary for that cycle. If the date of first patch application is missing but there is at least one entry for that cycle in the daily diary, the first day of the cycle will be derived from the study day and date of this entry. If the date of first patch application is missing and there is no entry for that cycle in the daily diary but at least one entry for that cycle in the weekly diary, the first day of the cycle will be derived from the study day and date of this entry.

The last day of a cycle coincides with the day before the start date recorded in the e-Diary for the next cycle.

However, because the last cycle of use has no start date for a following cycle, the last day of this cycle will be assumed to be 7 days after the date of last patch removal in the study or the last day of data entry whichever is later for subjects who completed the study. In case of early discontinued subjects, the last day of the last cycle will be assumed to be the date of last patch removal or the date of last data entry in the last cycle, whichever is later.

The last date of a cycle prior to in-between missing cycle(s) will be assumed to be 7 days after the last patch removal in the cycle or the date of last data entry, whichever is later.

The date of patch removal will be derived from the data collected in the e-Diary. In case of missing patch removal information, the last day of the cycle will be assumed to be 27 days after the start of the cycle or the date of last data entry in the cycle, whichever is later.

The last day of the last cycle of use should not be after the end of study participation date and the discontinuation date, respectively.

The start and stop dates of a cycle will be determined before determining whether the cycle is evaluable for the Pearl Index or for the bleeding data.

Evaluable cycles are defined as the complete or incomplete 28-day cycles in which vaginal intercourse occurred and in which no back-up contraception was used based on the e-Diary data. A cycle during which a woman became pregnant will be regarded as evaluable cycle even if back-up contraception was used or the woman did not confirm that vaginal intercourse occurred. Reported cycles after the cycle in which a pregnancy started according to the investigator will not be considered evaluable. Cycles beyond Cycle 13 will not be considered evaluable.

4.4.4 Extent of Exposure

The extent of total exposure of the study treatment during the study period will be determined by the total duration (in days) for which the study patches were used, the number of scheduled and unscheduled (replacement) patches used and the number of cycles in the study.

4.4.5 Pregnancy Related Definitions

Pregnancies will be classified as pre-, on-, or post-treatment based on the estimated date of conception, and in addition as method failure pregnancies. The definitions are provided below.

4.4.5.1 Pre-Treatment Pregnancies

Pre-treatment pregnancies are pregnancies with an estimated date of conception (EDC) prior to the date of the first study patch application.

4.4.5.2 On-Treatment Pregnancies

On-treatment pregnancies are pregnancies with an EDC between the date of first study patch application through Day 7 (inclusive) following removal of the last study patch (i.e., 7 days following the last documented day of patch wear).

4.4.5.3 Post-Treatment Pregnancies

Post-treatment pregnancies are pregnancies with an EDC that is after 7 days from the removal of the last study patch.

4.4.5.4 Method Failure Pregnancies

Method failure pregnancies are all on-treatment pregnancies of women who used the patch correctly and also had intercourse during the EDC cycle. Pregnancies are to be excluded from the calculation if the EDC is within any of the following cycles:

1. Cycles with reported partial (more than half of the patch lifts off the skin, but undetached) or complete patch detachment and meet the following:
    a. Subject did not replace patch within 24 hours or did not know how long the patch had been detached
2. Cycles with reported delayed/missed patch application:
    a. Did not place Cycle 1 Day 1 patch within 24 hours of menstruation (naïve users) or during the planned Cycle 1 Day 1 date (current hormonal contraceptive users) recommended by the investigator unless the first patch application was rescheduled to the next menstrual cycle
    b. Did not place Cycle 2 through 13 Day 1 patch on day 1 or was ≥48 hours late in changing Day 8 or Day 15 patch
3. Cycles immediately following points 1) and/or 2) started as a new cycle after an incomplete cycle
4. Cycles with reported major (key/important) Protocol Deviations (PDs) potential to have impact on contraceptive efficacy of the patch including the use of another contraceptive method

4.4.6 Bleeding Patterns

The e-Diary data will be used to characterize bleeding patterns. Bleeding data will be analyzed by cycle. Definitions for bleeding and spotting used for the analysis are provided in *Table* 4-2.

Table 4-2 Bleeding and Spotting Definitions

Terminology	Definitions
Bleeding	Evidence of blood loss that requires use of sanitary protection with a tampon, pad, or pantyliner
Spotting	Evidence of minimal blood loss that does not require new use of any type of sanitary protection, including pantyliners
Episode of bleeding/spotting	Bleeding/spotting days bound on either end by 2 days of no bleeding/spotting
Scheduled bleeding or withdrawal bleeding	Any bleeding/spotting that occurs during the patch-free interval and may continue into the first 4 days (Days 1-4) of the subsequent cycle
Unscheduled bleeding and Unscheduled spotting	Any bleeding or spotting episode that occurs when the subject is wearing the contraceptive transdermal patch with the following exceptions: • Bleeding/spotting episode that begins during a patch-free interval and continues through Days 1-4 of the subsequent active cycle will not be considered unscheduled • Any bleeding/spotting episode that is reported during Days 1-7 of the first cycle will not be considered unscheduled

4.5 Software

All report outputs will be produced using SAS® version [9.4] or a later version (if available at [redacted] in a secure and validated environment.

SDTM and SDTM IG versions will be as specified in DTMS while that of ADaM and ADaM IG versions will be as per analysis dataset specification document.

All report outputs will be provided to the Sponsor in RTF and PDF format. All listings will be shared in excel format as well.

4.6 Study Subjects

4.6.1 Disposition of Subjects

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion.

The subject disposition summaries may include the following:

- A summary of the number of subjects screened and enrolled and who were screened but not enrolled (i.e., screen failures) (Analysis set: All screened).

- The number and percentage of subjects enrolled but not treated and subjects who applied at least one patch in the study will be presented, together with the number and percentage of subjects who withdrew or discontinued from the treatment prematurely with a breakdown of the corresponding reasons for withdrawal. Additionally, the number and percentage of subjects who completed the study and the number and percentage of subjects who withdrew or discontinued from the study prematurely with the corresponding reasons for withdrawal will also be summarized.
- A separate disposition summary by analysis populations with the reasons for exclusion of subjects from a particular population will also be presented as frequency tabulation.

A by-subject listing of eligibility details, enrollment details, visit dates and withdrawal/study completion details (including reason for discontinuation), number of cycles completed will be provided. A similar by-subject listing for analysis populations will be presented.

4.6.2 Protocol Deviations

Protocol deviations (PDs) are defined as any failure to comply with the study protocol as approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC), whether planned or unplanned.

Major (key/important) PDs are those deviations from the protocol that are likely to have an impact on the subject's rights, safety, well-being, and/or on the integrity of the data for analysis. This will include all important deviations to be reported in the CSR.

Major (key/important) PDs and any action to be taken regarding the exclusion of subjects or affected data from specific analyses are defined in the project-specific PD Specification.

The defined PDs will be collected during the study period by site monitor/clinical team and programming team. These may include:

- Violation of study inclusion or exclusion criteria
- Any procedural and study conduct deviations (including Investigational Product (IP) related deviations) recorded on a PD log/patient's study record
- All delayed and missed visits
- Use of prohibited medication unauthorized by protocol
- Corona Virus Disease 2019 (COVID-19) related deviations

PDs and analysis sets will be reviewed in the data review meeting after last patient last visit and before the database lock to decide inclusion or exclusion of participant(s) from analyses sets. Decisions regarding the exclusion of participants and/or participant data from analyses will be made prior to database hard lock and will be documented and approved.

A by-participant listing of major (key/important) and minor (non-important) PDs will be provided including participant identifier, PD classification, and PD description.

A separate by-participant listing for COVID-19 related deviations will be presented.

4.7 Analysis Sets

The following analysis populations are defined in this study:

1. All-enrolled population: All subjects who were enrolled into the study (i.e., subjects who had a non-missing enrollment date on the enrollment page of the CRF).
2. Safety population: All subjects who had at least one study patch application after enrollment.
3. Contraceptive efficacy population (CEP): All subjects in the safety population who have a negative enrollment serum β-hCG at enrollment visit. If the test was missed to be performed due to unforeseen reasons, results if available from UPT found to be negative at enrollment visit, can be considered for inclusion in the CEP.
4. Cycle control population: All subjects in CEP who provide any information on bleeding and patch application in e-Diary.
5. Efficacy evaluable (EE) population: All subjects in CEP aged 16 to 35 years (inclusive) at enrollment who have a baseline BMI <30kg/m^2 and have at least one efficacy evaluable cycle.

   An efficacy evaluable cycle is a cycle that meets any of the following criteria:

   - Cycle in which vaginal intercourse occurred and in which no backup or emergency contraception was used based on e-Diary data
   - Cycle in which a pregnancy occurred

4.8 Demographic and Other Baseline Characteristics

The demographic and baseline characteristics at study entry will be summarized for the safety population and Efficacy Evaluable (EE) population, respectively.

The summaries provided may include the following:

- A summary of demographic variables including age (<18 years, 18-35 years, >35 years), race, ethnicity, educational status, country, height, body weight (<70 kg, 70-90 kg, ≥90kg), BMI (<25 kg/m^2, ≥25 to <30kg/m^2, ≥30kg/m^2), tobacco substance use (current, previous, and never) by category

If subjects record more than one race, then for the summary table, these subjects will be included in the Other Race group.

- A summary of other possibly relevant variables such as a general medical, gynecological, obstetric history including menstrual and medication history, and previous hormonal contraceptive method use variables (e.g., age at menarche, typical length of menstrual cycle, typical duration of menses, total number of pregnancies, number of abortions, contraceptive use by category such as naïve users, prior users, recent users, and current users)

Age will be calculated as the number of complete years between a subject's birth date and the date of informed consent. For the purposes of the analyses on this study, age at enrollment will be considered the same as the age at informed consent.

Age, height, weight and BMI will be summarized using the mean, SD, minimum, median, and maximum. The count and percentage will be computed for race, and ethnicity. Age (<18, 18-35, >35), body weight (<70, 70-90, ≥90) and BMI (<25, 25-<30, ≥30) will be presented by categories.

A by-subject listing for demographic and baseline characteristics will be presented for safety population.

A by-subject listing for a general medical, contraceptive use, obstetric & gynecological history including menstrual and medication history will be presented for the safety population.

Gynecological/Menstrual/Pregnancy/Contraceptive History:

The gynecological, menstrual and pregnancy history variables listed below will be summarized for the safety population and EE population, respectively.

- Menstrual variables (reported as continuous variables)
  - Age at menarche (years)
  - Typical length of menstrual cycle (days)
  - Typical duration of menses (days)
- Pregnancy variables (reported as continuous variables and as a frequency for each value)
  - Total number of pregnancies
  - Pregnancy outcomes
- Number of deliveries
  - Full-term liveborn
  - Preterm liveborn
  - Stillbirth/intrauterine demise ≥20 weeks
- Number of abortions (elective)
- Number of abortions (spontaneous)
- Number of ectopic pregnancies

The latest assessment will be used in the summaries.

Any variables that are given as '<xx', '>xx', '<=xx', '>=xx' in the database will be imputed with the absolute value of the number without the sign (e.g., <2.2 will be imputed as 2.2) for the calculation of the descriptive statistics. In the listings, no imputations will be performed, and all data will be displayed as recorded in the database.

Contraceptive use and contraceptive use status will be summarized for the safety population and EE population, respectively. Both the Screening and the Enrollment assessments will be used for these summaries.

Any past medical condition or a medical condition that is present at the time that the participant is screened will be considered as baseline medical history. Medical history will be coded using MedDRA, Version 25.1 or latest. Medical history will be summarized at system organ class (SOC) and preferred term (PT) levels for the safety population. Medical history information will be reported in a data listing. The listing will show each verbatim term (i.e., term reported by the investigator), as well as the SOC and PT associated with the verbatim term.

4.9 Prior and Concomitant Medication

Medications other than study drug will be coded by the World Health Organization (WHO) Drug Dictionary, (Version September 2022 B3 or latest) and summarized by Anatomical Therapeutic Chemical Level 3 (ATC-3) code and preferred name.

Medications will be included in the concomitant medication summary if they were taken between the first patch application and the removal of the last patch, inclusive. All post-study contraceptives taken by subjects will be included and identified as post-study treatment medications. Medications taken prior to first application of study medication will be documented as a prior medication.

Medications starting prior to first patch application and continuing during the study will be considered both prior and concomitant medication.

The number and percentage of subjects reporting each ATC-3 code and each preferred name will be summarized for concomitant medications. A subject who reports the use of two or more medications with the same preferred name will be counted only once for that preferred name. A subject who reports the use of two or more medications with the same ATC-3 code will be counted only once for that ATC-3 code. No statistical comparisons are planned.

A by-subject listing of prior and concomitant medications will be provided for the safety population.

4.10 Treatment Compliance

The proportion of cycles with "perfect compliance" will be reported.

Cycle with "perfect compliance" is defined as having at least 21 days of consecutive patch wear with no patch worn for more than 9 days.

In addition, the proportion of cycles with 21, 15-21 and less than 15 consecutive days of patch wear will be presented.

The cycle-wise e-Diary compliance will be presented for the treatment daily diary. This will be estimated as proportion of actual number of days of data entry out of the expected number of days of data entry. The expected number of days is defined as the number of days between each woman's first reported patch application through the last day of the cycle for each cycle.

A by-subject listing of treatment and e-Diary compliance data will be provided.

4.11 Efficacy Evaluation

4.11.1 Primary Efficacy Variable – Pearl Index

The primary contraceptive efficacy variable is Pearl Index (PI) in EE population aged 16 to 35 years (inclusive) and BMI <30 kg/m^2. PI is defined as the number of pregnancies per 100 women-years and will be calculated by multiplying number of on-treatment pregnancies by 1300 (for 13 cycles in a year) and divided by the number of 28-day evaluable cycles.

$$\text{Pearl Index} = \frac{number\ of\ on{-}treatment\ pregnancies \times 13}{number\ of\ evaluable\ cycles} \times 100$$

where,

- On-treatment pregnancy is defined as the pregnancy with an EDC between the date of application of the first patch through 7 days after the removal of the last patch in the study.
- Evaluable cycles are defined as the complete or incomplete 28-day cycles in which vaginal intercourse occurred and in which no back-up contraception was used based on the e-Diary data unless a pregnancy occurred in such a cycle.

Reported cycles after the cycle in which a pregnancy started according to the investigator will not be considered evaluable.
Cycles beyond Cycle 13 will not be considered evaluable.

The assessment of efficacy will be based on point estimate and 95% CI for the PI.

The CI will be calculated using a Poisson distribution. The CI limits will be calculated by the following equations:

$$CL_{lower} = \frac{\frac{1}{2}\chi^2_{0.025,2x}}{number\ of\ evaluable\ cycles} \times 1300$$

$$CL_{upper} = \frac{\frac{1}{2}\chi^2_{0.975,2(x+1)}}{number\ of\ evaluable\ cycles} \times 1300$$

where x is the number of on-treatment pregnancies and $\chi^2_{alpha,\,df}$ is the alpha quantile from chi-square distribution with df degrees of freedom.

The primary efficacy analysis will be performed on the EE population as defined in Section 4.7.

For the primary efficacy analysis, PI will be calculated utilizing the number of on-treatment pregnancies adjudicated by the PRC.

Based on the EDC in relation to the date of last patch removal, each confirmed pregnancy is classified as: Pre-treatment pregnancy, On-treatment pregnancy, and Post-treatment pregnancy.

A summary table will report the total number of pregnancies and the number of pre-, on-, and post-treatment pregnancies for safety population.

An additional analysis will be performed based on the medical monitor's determination of EDC. The calculations will be also done for all women in CEP. The PI in CEP will include >35 years and obese (≥30 kg/m^2) population.

Number of pregnancies, number of evaluable cycles, the PI and corresponding 95% CIs will be presented by the subgroups described in Section 4.3.7 for EE population, including a forest plot for the BMI based subgroup analysis. All subject diary data, pregnancy information and evaluable cycles for each analysis will be listed.

A sensitivity analysis will be conducted by including cycles without sexual activity and cycles with back-up contraception.

[redacted]

4.11.2 Secondary Efficacy Variables

1. Cycle-wise and cumulative pregnancy rates over 1 year evaluated using life table analysis

Cycle-wise and gross cumulative probability of pregnancy will also be measured using a life table analysis on the EE population. The analysis will be done for all pregnancies and for all Method Failure (MF) pregnancies. The endpoint of primary interest is the cumulative probability of pregnancy at the end of Cycle 13. Cycles beyond Cycle 13 will not be used. The cumulative probability of pregnancy will be presented by cycle, along with the number of pregnancies occurring in each cycle and the two-sided 95% CI for the cumulative probability of pregnancy. Non-pregnant subjects will be censored in their last reported cycle. The life table analyses will be implemented by using the Kaplan-Meier method within PROC LIFETEST of SAS. The 95% CIs will be calculated using the Greenwood

formula for the variance with a loglog transformation. The estimated life table cumulative pregnancy rate through Cycle 13 will be presented by cumulative probability graph by cycle along with the number of pregnancies occurring in each cycle and the two-sided 95% CI for the cumulative probability of pregnancy.

Life table analyses will be performed for the same subgroups as those reported for the Pearl Index.

2. Method failure PI

The separate calculation of the PI for method failure will exclude pregnancies in non-compliant cycles from the numerator and the non-compliant cycles from the denominator.

The method failure PI and corresponding 95% CI will be calculated in the EE population. It will be analyzed using the same method as primary variable but includes only those pregnancies that were classified as method failure.
The method failure PI is defined as PI among all complete or incomplete evaluable cycles in which intercourse occurred and excluding the following:

1) Cycles with reported partial (more than half of the patch lifts off the skin, but undetached) or complete patch detachment and meet the following:
    a. Subject did not replace patch within 24 hours or did not know how long the patch had been detached
2) Cycles with reported delayed/missed patch application:
    a. Did not place Cycle 1 Day 1 patch within 24 hours of menstruation (naïve users) or during the planned Cycle 1 Day 1 date (current hormonal contraceptive users) recommended by the investigator unless the first patch application was rescheduled to the next menstrual cycle
    b. Did not place Cycle 2 through 13 Day 1 patch on day 1 or was ≥48 hours late in changing Day 8 or Day 15 patch
3) Cycles immediately following points 1) and/or 2) started as a new cycle after an incomplete cycle
4) Cycles with reported major (key/important) PDs potential to have impact on contraceptive efficacy of the patch including the use of another contraceptive method

Characterization of pregnancies:

A summary table will report the total number of pregnancies and the number of pre-, on-, and post-treatment pregnancies.

The number and percentage of on-treatment pregnancies associated with each category for the following parameters will be summarized by age, cycle in which pregnancy occurred, BMI category, previous hormonal contraceptive use status, race, ethnicity, educational status, weight, previous pregnancy history.

On-treatment pregnancies will be classified as MF based on available patch wear information.

A listing of pregnancies occurring among all safety subjects including patch wear dates, pelvic examination results, ultrasound(s) results, and the EDC as determined by the investigator. Additionally, a listing of pre-, on- and post-treatment pregnancies as classified by the PRC and a listing of pre-, on- and post-treatment pregnancies as classified by the medical monitor will be presented.

4.12 Safety Evaluation

All safety summaries and analyses will be based upon the Safety population as defined in Section 4.7.

Safety assessments, including AEs, clinical laboratory evaluations, vital sign measurements, targeted physical and gynecological examinations, patch wearability (i.e., patch adhesion and application site irritation), and concomitant medication use, will be presented in data listings and/or summarized with descriptive statistics.

Safety parameters and other metrics may be further summarized by previous contraceptive use status, BMI category, age group, race, and ethnicity.

4.12.1 Extent of Exposure

The treatment exposure will be summarized for the safety population based on the use of the study patch, duration of use and cycle.

Treatment exposure will be summarized by the duration over which the patch was used, the number of patches used per cycle and the number of cycles which utilized "n" patches in the study.

1. The exposure duration per cycle is determined as: date of last patch removal in the cycle – date of 1st patch application in the cycle + 1 – missed patch application days. The duration of exposure during the study will be determined as sum of durations of exposure from all the cycles.
2. The total number of patches used by each subject will be presented as descriptive statistics (mean, median, minimum, and maximum) using
    a. Number of scheduled patches used
    b. Number of unscheduled (replacement) patches used
    c. Reasons for unscheduled patch changes/replacement such as
        i. patch fell off/detached
        ii. patch accidently pulled off
        iii. removed because of skin irritation or itching
        iv. removed for other personal reasons
        v. preference for different location on body
        vi. unknown
3. Number of cycles which used "n" patches in the study
4. Proportion of patients completed at least 'n' number of cycles for the first through the last cycle
5. Summary statistics for the number of cycles (mean, standard deviation, median, max, min) will be provided

Cycles beyond Cycle 13 will be presented in the exposure summary table.

A by-subject listing of exposure data will be provided for each cycle.

4.12.2 Adverse Events (AEs)

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1 or higher.

Treatment-emergent adverse events (TEAEs) will be tabulated and are defined as those AEs that either start or worsen in severity on or after the date/time of first patch application through the last day of the subject's final treatment cycle.

An overall AE summary will be provided by the number and percentages of subjects reporting at least one TEAE and the total number of events reported, for safety population.

These will generally include the following summaries:

- A summary of the number and percentage of subjects reporting a TEAE by SOC, and PT
- A summary of the number and percentage of subjects reporting a TEAE by maximum causality by SOC and PT
- A summary of the number and percentage of subjects reporting a TEAE by severity, SOC and PT

AE summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC, and then alphabetically for SOC, and PT within SOC. A subject who has multiple events in the same SOC and PT will be counted only once in the subject counts, but all events will be included.

For each subject and each AE, the worst severity recorded will be attributed and used in the by-severity summaries. Similarly, the worst causality (most related to treatment) will be attributed and used in the by-causality summaries. If causality is missing, a conservative approach for AE assessment (considering the worst case) will be followed. Severity will be categorized as mild, moderate, or severe. Relationship to study drug will be categorized as unrelated, unlikely related, possibly related, probably related, and definitely related.

A by-subject listing of all AEs will be provided. This listing will be presented by subject identifier, age, race, adverse event (SOC, PT, and verbatim term), application site reaction, date of onset, date of resolution, severity, seriousness, action taken, outcome and causality. AEs related to hormone, bleeding related AEs and VTEs will be flagged in separate columns in the listing.

AEs may be further summarized by previous contraceptive use status, BMI, race, ethnicity, and age group.

4.12.3 Deaths, Serious Adverse Events (SAEs), and Other Significant Adverse Events

SAEs (including events with an outcome of death) will be listed by subject. Other significant AEs are those AEs reported as leading to study treatment interruptions (including discontinuations).

The following summaries may be included:

- A summary of the number and percentage of deaths during the study, (if numbers allow)
- A summary of the number and percentage of subjects reporting a TESAE by SOC and PT in decreasing frequency order
- A summary of number and percentage of subjects with non-serious TEAEs by SOC and PT.
- A summary of the number and percentage of subjects with TEAEs leading to study medication discontinuation by SOC and PT in decreasing frequency order
- Separate summary table for treatment emergent bleeding AEs for safety population (PTs like metrorrhagia, menorrhagia, vaginal hemorrhage, dysmenorrhea, menstruation irregular, dysfunctional uterine bleeding, menstrual disorder) will be presented by SOC, PT.
- A summary table for treatment emergent hormone AEs will be presented by SOC and PT
- A listing of subjects with potential treatment emergent VTE will be presented.
- A separate table for application site disorder TEAEs by PT (any TEAE, severe TEAE, drug related TEAE, SAE, TEAE resulting in discontinuation of study medication)
- Incidence of most common TEAEs reported by ≥2% subjects will be presented

Summaries by SOC and High-Level Group Term (HLGT) may also be presented.

The following listings may be included:

- A by-subject listing of all deaths that occurred during the study
- A by-subject listing of all SAEs
- A by-subject listing of all AEs leading to discontinuation of study treatment
- A by-subject listing of all other significant AEs (when none of the other seriousness criteria apply to the event but the investigator still considers the event as serious)

4.12.4 Bleeding and Spotting

Cycle control will be evaluated using data from the e-Diary, and will be summarized for all cycles, including incomplete (i.e., those with < 100% method utilization) cycles and cycles with incomplete bleeding information.

For each cycle and for all cycles combined, the following parameters will be summarized using descriptive statistics (mean, median and range):

- Number of bleeding and/or spotting days
- Number of bleeding-only days
- Number of spotting-only days
- Number of unscheduled bleeding and/or spotting days
- Number of unscheduled bleeding-only days
- Number of unscheduled spotting-only days
- Number of scheduled days of bleeding and/or spotting
- Number of scheduled bleeding-only days
- Number of scheduled spotting-only days

For each cycle and for all cycles combined, the following parameters will be summarized:

- Number of days with no bleeding and/or spotting
- Number and percentage of subjects with complete absence of bleeding and/or spotting (i.e., 0 days of bleeding or spotting)
- Number of bleeding and/or spotting episodes
- Number of bleedings only episodes
- Number of spotting episodes

Incidences (percentage of subjects) of unscheduled bleeding and/or spotting episodes within each cycle will be reported; incidence will be calculated as number (n) of subjects with unscheduled bleeding and/or spotting among the number (N) of subjects in the cycle control population.

A bar chart of the incidence of unscheduled bleeding and/or spotting episodes for all the cycles will be presented as per recommendations by Mishell et al., 2007a.*[1]*

For evaluation of bleeding patterns over time, an analysis including only subjects who completed the study as well as an analysis of the cycle control population will be conducted.

A separate subgroup analysis of cycle control profile will be conducted and reported for subjects who discontinued the study prematurely due to unacceptable bleeding. Subjects who had unacceptable

bleeding are subjects who had a bleeding adverse event which led to a discontinuation of the study drug.

Analysis of cycle control will also be performed for the subgroups based on the variables BMI, weight, age, parity, history of prior hormonal contraceptive use.

4.12.5 Clinical Laboratory Evaluation

Clinical laboratory test results (hematology, serum biochemistry, urinalysis, UPT, SPT, chlamydia and gonorrhea screening, HIV testing, cervical cancer screening and urine drug screen parameters) will be listed by subject and study visit including changes from baseline (except for categorical urinalysis tests, urine drug tests, chlamydia and gonorrhea, HIV testing and cervical cancer screening).

All TLFs will display only the standard international units after conversion by means of standard conversion factors.

Quantitative clinical laboratory variables, i.e., hematology, biochemistry, and urinalysis will be summarized using descriptive statistics (n, mean, SD, minimum, maximum, and median). Additionally, a within-participant change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way.

Any quantitative laboratory parameters that are given as '<xx', '>xx', '<=xx' or '>=xx' in the database will be imputed with the absolute value of the number without the sign (e.g., <2.2 will be imputed as 2.2) for the calculation of the changes from baseline and for the descriptive statistics. In the listings, no imputations will be performed, and all data will be displayed as recorded in the database.

Each laboratory result will be classified as low, normal, or high at each time point according to the laboratory supplied reference ranges. The investigator will assess whether the values outside the clinical reference range are clinically significant, and these will be reported as abnormal not clinically significant (NCS) or abnormal clinically significant (CS). Clinically significant laboratory values will be recorded by the investigator as AEs.

Shift tables will be presented for continuous laboratory parameters (serum biochemistry and hematology) showing the number and percentage of subjects with shifts from baseline to each post-baseline visits.

The assessment of categorical urinalysis variables will be tabulated by visit for each urine parameter in frequency tables.

4.12.6 Vital Signs, Physical Findings and Other Observations Related to Safety

4.12.6.1 Vital Signs

A by-subject listing and a summary of all vital sign measurements (including weight) and change from baseline will be presented.

Measured (observed) values including the number and percentage of subjects with potentially clinically significant changes in vital signs (*Table 4-3)* after the first day of patch wear will be summarized by vital sign parameter (BP and pulse rate).

The table will list all subject's values for parameters meeting the criteria.

Table 4-3 TEMA/PCS Criteria for Vital Signs

Variable	Unit	Criterion	
		Low	High
Systolic blood pressure	mmHg	≤80 mmHg and ≥20 mmHg decrease from Baseline	≥140 mmHg and ≥20 mmHg increase from Baseline
Diastolic blood pressure	mmHg	Value ≤60 and ≥15 decrease from Baseline	Value ≥90 and ≥15 increase from Baseline
Pulse rate	bpm	Value ≤40 and ≥15 decrease from Baseline	Value ≥90 and ≥15 increase from Baseline

Note: The change in measurement (increase or decrease) will be calculated relative to the value obtained at baseline.

Both conditions must be satisfied for a measurement to be considered potentially clinically significant; bpm = Beats per minute.

4.12.6.2 Targeted Physical and Gynecological Examination

Results of physical and gynecological examination are recorded as "normal" or "abnormal" for each body system. The targeted physical examination will consist of an examination of the abdomen, cardiovascular system, chest/lungs, neurological systems, skin, musculoskeletal/extremities, and thyroid gland.

The gynecological examination will include an evaluation of the following: breast examination (performed by palpation/observation) and assessment of the adnexa, cervix, uterus, vagina, and external genitalia.

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

4.12.6.3 Patch Adhesion and Patch Application Site Irritation

Patch adhesion and application site irritation will be evaluated by examination of the patch application site by the investigator or designee at each scheduled visit, as per Table 6-1. Subjects will also report patch adhesion and application site irritation daily in the e-Diary.

Subjects will also record patch application/patch change timing and anatomical placement and daily exposure of the patch to water.

Patch Adhesion

Investigators will rate patch adhesion using the following 5-point scale:

Table 4-4 Investigator's Scoring System of Patch Adhesion Assessment during Clinic Visits

Score	Definition
0	≥90% adhered (i.e., the TDS has essentially no lift off the skin)
1	≥75% adhered but <90% (e.g., only some edges of the TDS lift off the skin)
2	≥50% adhered but <75% (i.e., less than half of the TDS lifts off the skin)
3	>0% to <50% (i.e., the TDS is not detached, but more than half of it lifts off the skin without falling off)
4	0% adhered (i.e., the TDS is detached and is completely off the skin)

Subjects will report patch adhesion in their e-Diary on all days except during the patch-free week on the following 5-point scale:

Table 4-5 Self-Reported Scoring System of Patch Adhesion Assessment

Score	Definition
0	The patch has essentially no lift off the skin (≥90% adhered)
1	Only some edges of the patch lift off the skin (≥75% to <90% adhered)
2	Less than half of the patch lifts off the skin (≥50% to <75% adhered)
3	The patch is not detached, but more than half of it lifts off the skin without falling off (>0% to <50% adhered)
4	The patch is detached and is completely off the skin (0% adhered)

The total number and percentages of patches applied to each anatomical region will be summarized by cycle and overall.

The number of patches exposed to water and the number of subjects wearing patches exposed to water will be summarized by cycle and overall.

The reported adhesion score by investigator will be summarized by visit for each patch application site and overall using frequency distributions. Subject assessments of patch adhesion will be summarized at both the subject and patch level by cycle and overall, for each application site and overall using frequency distributions. On the subject level, the maximum adhesion score (AS) reported by a woman in a cycle or overall will be assessed. On the patch level, the maximum AS reported for a patch will be assessed. For each patch, the maximum AS will be calculated based on the maximum AS observed within patch on days within a cycle. The within-cycle max AS for any subject is the maximum AS for all patch AS of the subject for the given cycle. The overall max AS for a subject is the maximum AS of all AS for the subject during all the cycles a subject had.

Patch Application Site Irritation

Investigators will rate patch site skin irritation using the following criteria:

Table 4-6 Assessment of Skin Irritation - Investigator's Scoring System

Score	Definition
None	No irritation or barely perceptible/spotty erythema
Mild	Mild erythema covering most of the application site
Moderate	Moderate erythema, possible mild edema
Severe	Severe erythema, possible edema, vesiculation, bullae and/or ulceration

The degree of patch site skin irritation will be reported daily by subjects in the e-Diary. Irritation will be scored as:

Table 4-7 Self-Reported Scoring System of Application Site Irritation Assessment

Score	Definition
None	No irritation or barely seen/very minimal skin redness
Mild	Minimal skin redness covering most of the application sites
Moderate	More than minimal skin redness, possible minimal swelling
Severe	Intense skin redness, possible swelling, rashes, blisters, and/or broken skin

Investigator-reported patch site skin irritation scores will be reported by visit using frequency distributions. Investigator-reported skin irritation summaries will be further reported by per application site.

Subject assessments of patch site skin irritation will be tabulated using frequency distributions for all patch applications within individual cycles and for all patch applications for all cycles combined. The worst subject-reported skin irritation scores will be reported in the summaries for individual cycles and for all cycles combined. On the subject level, the maximum score reported by a woman in a cycle or overall will be assessed. Skin irritation summaries will be further summarized by patch application site.

4.12.7 Safety Monitoring (Independent Data Monitoring Committee [IDMC], Data Monitoring Committee [DMC], Data and Safety Monitoring Board [DSMB])

Not applicable for this study.

4.13 Other Analyses

4.13.1 Pharmacokinetics

Pharmacokinetics (PK) sampling will be done for subjects reporting any suspected or confirmed arterial or venous thromboembolic event.

All possible attempts should be made to collect PK samples as soon as possible in the event of any suspected or confirmed arterial or VTEs. The blood samples will be analyzed for ethinyl estradiol and norelgestromin concentrations using fully validated analytical methods.

By-subject listings of these data should be provided.

4.14 Determination of Sample Size

Approximately 1,200 eligible women enrolled and treated for up to 13 cycles are expected to provide at least 10,000 evaluable cycles for safety.

The study population will be selected such that:

- The proportion of non-white study participants will be at least 30% of the total study population to reflect the general population in the US
- The proportion of women over the age of 35 years will represent approximately 10% of the total study population
- The proportion of women with higher BMI ($\geq$30 kg/m^2) will be capped to a maximum of 10% of the total study population

Based on the assumptions above, it is expected that approximately 1,000 enrolled women aged 16 to $\leq$35 years and with BMI <30 kg/m^2 will provide at least 5000 evaluable cycles (after excluding cycles with back-up contraception and abstinent cycles, unless a pregnancy occurred in such a cycle) for efficacy. [redacted]

At least 200 subjects will complete the study.

4.15 Changes in the Conduct of the Study or Planned Analysis

No changes.

4.16 Post Hoc Supporting Analyses

[redacted]

5 REFERENCES

Journals:

[1] Mishell Jr. DR, Guillebaud J, Westhoff C, et al. Combined hormonal contraceptive trials: variable data collection and bleeding assessment methodologies influence study outcomes and physician perception. Contraception. 2007a;75:4-10.

Software:

[2] SAS® Version 9.4 of the SAS System for Personal Computers. Copyright ©2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

6 APPENDICES

Table 6-1 Schedule of Assessments

Visits	Screening[1]	Enrollment[1]	Cycle 1/ TFU	Cycle 2	Cycle 3/ TFU	Cycle 4/ TFU	Cycle 5	Cycle 6/ TFU	Cycle 7/ TFU	Cycle 8	Cycle 9/ TFU	Cycle 10/ TFU	Cycle11/ TFU	Cycle 12	Cycle 13/ TFU	EOS/ ET[2]
Treatment Cycle Day	7 to 60 days prior to enrollment	Between Day -14 to Day -1 of Cycle 1 Day 1	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	14 (+5) days after patch removal
Informed consent/assent	✓															
Inclusion/ exclusion criteria	✓	✓														
IWRS Registration with assignment of Subject Identification Number	✓															
Demography[3]	✓															
Medical & Surgical and Medication History[4]	✓															
Gynecological, Obstetric, Menstrual & Contraceptive Use History[5]	✓	✓														
Alcohol abuse, Smoking & drugs of abuse history	✓															
Targeted Physical Examination including Gynecological examination	✓															✓
Height[6], Weight, BMI	✓	✓								✓						✓
Vital signs (BP, RR, PR, Temperature)	✓	✓		✓			✓			✓				✓		✓
Laboratory Investigations[7]	✓															✓
Urine drug screen	✓															
Testing for Chlamydia trachomatis and Neisseria gonorrhea	✓															
Cervical cancer screening[8]	✓															
Confirm and validate current cycle with e-Diary entry			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Visits	Screening[1]	Enrollment [1]	Cycle 1/ TFU	Cycle 2	Cycle 3/ TFU	Cycle 4/ TFU	Cycle 5	Cycle 6/ TFU	Cycle 7/ TFU	Cycle 8	Cycle 9/ TFU	Cycle 10/ TFU	Cycle11/ TFU	Cycle 12	Cycle 13/ TFU	EOS/ ET [2]
Treatment Cycle Day	7 to 60 days prior to enrollment	Between Day -14 to Day -1 of Cycle 1 Day 1	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	14 (+5) days after patch removal
Confirm and validate Day 1 of the current cycle with e-Diary entry			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Urine Pregnancy Test (UPT)[9]	✓	✓	✓	✓			✓			✓				✓		✓
Serum Pregnancy test (SPT)[10]		✓														✓
Pregnancy determination[11]			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medication			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dispense run-in e-Diary with subject training	✓															
Dispense condoms and spermicide [12]	✓													✓		
Collect unused condoms [13]																✓
Run-in e-Diary compliance check		✓														
Dispense Study Patch (including reserve patches as required) with instructions		✓[13]		✓			✓			✓				✓		
Dispense study e-Diary with subject training		✓														
Dispense home urine pregnancy kits[14]		✓		✓			✓			✓				✓		
Review compliance (including e-Diary use, patch use, back-up contraception, sexual activity) and re-training of subject as necessary			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Investigator's evaluation of patch application site				✓			✓			✓				✓		✓
Investigator's evaluation of patch adhesion[15]				✓			✓			✓				✓		
Adverse events recording	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Intention to plan for pregnancy[16]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Review contact information	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Post-treatment contraceptive counselling														✓[17]		✓

Visits	Screening[1]	Enrollment[1]	Cycle 1/ TFU	Cycle 2	Cycle 3/ TFU	Cycle 4/ TFU	Cycle 5	Cycle 6/ TFU	Cycle 7/ TFU	Cycle 8	Cycle 9/ TFU	Cycle 10/ TFU	Cycle11/ TFU	Cycle 12	Cycle 13/ TFU	EOS/ ET[2]
Treatment Cycle Day	7 to 60 days prior to enrollment	Between Day -14 to Day -1 of Cycle 1 Day 1	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	14 (+5) days after patch removal
Blood Samples for PK[18]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

C1D1: Cycle 1 Day 1; TFU: Telephonic Follow-up visit; EOS: End of Study; ET: Early Termination; IWRS: Interactive Web Response System; BMI: Body Mass Index; BP: Blood Pressure; RR: Respiratory Rate; PR: Pulse Rate; e-Diary: Electronic Diary

1. Screening period should be at least for 7 days before enrollment. Enrollment will be performed between Day -14 to Day -1 before the start of next expected menstrual cycle; if the first study patch is applied at the site, this will be the Cycle 1 Day 1 for the subject If the first study patch was applied at the site during the enrollment visit, a follow-up telephonic visit still needs to be conducted until Day 15 of Cycle 1.
2. EOS Visit must be performed at 14 (+5) days after removal of last patch.
   In case of an early discontinuation from the study, whenever possible, it is recommended that ET visits be performed at 14 (+5) days after removal of last patch. However, this can be performed earlier based on subject's convenience in visiting the site and/or at the investigator's clinical decision.
3. Includes date of birth, age, race, ethnicity, educational status.
4. Medical History: Including check of VTE risk; Medication History: See section 5.8 on concomitant medications
5. At screening visit: Full details of contraceptive use history should be recorded for the year prior to screening. If relevant, medical/contraceptive history more than one year also need be collected; At enrollment visit: Only the history during screening period needs to be collected.
6. Height is measured at screening visit (ONLY), for all subjects. At all other visits, height is measured only for adolescent subjects (i.e., <18 years of age).
7. Blood samples for hematology, chemistry, HIV testing and urine samples for urinalysis will be obtained; samples for chemistry should be taken under fasting conditions; Note: HbA_1C and HIV testing ONLY at screening visit.
8. Cervical cancer screening: will not be performed for subjects < 21 years of age; for women aged 21 to 29 years, pap test will be performed, pap test may be followed by reflex HPV if needed; for ≥30 years, HPV and cytology will be performed; for all subjects, cervical cancer screen test results are acceptable from previous testing if they are available from testing within last 6 months of screening.

9. UPT will be performed at screening, at enrollment visit, before start of first ever study patch application (if applied at home), at all clinic visits and whenever subject is at risk of pregnancy or pregnancy is suspected (for example, any symptoms/signs suggestive of pregnancy, missed/ delayed patch application during that cycle without use of a back-up contraception as per requirements). In case of indeterminate or positive UPT result, SPT, pelvic examination and transvaginal ultrasound must be performed at the earliest possible time, preferably on the same day.
   Note: If subject has a positive UPT at screening or at enrollment visit, subject will be screen failed; such pregnancy would be designated as a pre-treatment pregnancy
10. Results of SPT testing at the enrollment visit may be available after the first patch has been placed. If subject has a positive SPT at enrollment visit, subject will be discontinued from study and counselled on continuation of pregnancy and on further standard medical care; such pregnancy would be designated as a pre-treatment pregnancy. If subject has a positive SPT at ET or EOS visit, subject will be asked to return to the study site and pelvic examination and transvaginal ultrasound will be performed at the earliest possible time, preferably the same day. If the subject applies her first patch later than 7 days from the enrollment visit, the subject should contact the site immediately after first patch application to schedule a visit to perform a SPT (even if the UPT is negative before first patch application) within 7 days from the first patch application.
11. Pregnancy determination only if UPT is positive/indeterminate; SPT and pelvic examination will be performed at the earliest possible time, preferably same day of the UPT result is positive or indeterminate; it is highly recommended that an early transvaginal ultrasound examination is performed on the same day of the UPT.
12. For all women, condoms and spermicide will be dispensed at screening visit to be used during the screening period and up to first patch placement; based on the availability with subjects, condoms and spermicide will be dispensed at the cycle 12 visit for use after patch free week of cycle 13 in addition to any planned/actual start of any contraceptive method; Unused condoms will be collected at EOS visit. Subjects who prematurely terminate study drug will be asked to use barrier methods of contraception such as condoms and spermicide or diaphragm and spermicide until completion of the ET visit.
13. For subjects who will apply their first study patch later at home, a demonstration patch (no active ingredients) will be used to train the method of patch application.
14. UPT kits would be dispensed based on availability of UPT kit with the subject.
15. Adhesion performance should not be evaluated if the subject is not wearing the patch during the clinic visit.
16. The subject will be asked at each visit if she has a desire to become pregnant. In case of a positive answer, the subject will be discontinued from further study participation.
17. Includes instructions to use barrier contraceptives after the patch-free week of cycle 13 in addition to any planned/actual start of contraception including CHCs through the end of study visit.
18. All possible attempts should be made to collect PK samples as soon as possible in the event of any suspected or confirmed arterial or venous thromboembolic events. The blood samples will be analyzed for ethinyl estradiol and norelgestromin concentrations using fully validated analytical methods.

[redacted]

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