# Statistical Analysis Plan

**Medicines360**

**Protocol: M360-L102**

A Phase 3, Multi-Center, Open-Label Study of a Levonorgestrel-Releasing Intrauterine System for Long-Term, Reversible Contraception

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| ANCOVA | analysis of covariance |
| AR1 | first-order autoregressive |
| ATC | Anatomical Therapeutic Chemical |
| BLQ | below the level of quantification |
| BMI | body mass index |
| BP | blood pressure |
| CI | confidence interval |
| cm | centimeter(s) |
| CM | Concomitant Medication |
| CRF | case report form |
| CS | clinically significant |
| CSR | clinical study report |
| DDE | drug dictionary enhanced |
| DRUP | FDA Division of Reproductive and Urological Products |
| EP | Ectopic pregnancy |
| ET | endometrial thickness |
| g | gram(s) |
| HEENT | head, eye, ear, nose, and throat |
| IDMC | Independent Data Monitoring Committee |
| in | inch(es) |
| IUS | intrauterine system |
| kg | kilogram(s) |
| lb | pound(s) |
| l | Liter |
| LNG | Levonorgestrel |
| LS | least-square |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Mg | milligram(s) |
| MITT | Modified Intent-to-Treat |
| NDA | new drug application |

**LIST OF ABBREVIATIONS (continued)**

| | |
|---|---|
| Ng | nanogram |
| PK | Pharmacokinetics |
| PP | Per-Protocol |
| RTF | rich text format |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SAS | SAS® Software |
| SD | standard deviation |
| SE | standard error |
| TEAE | treatment-emergent adverse event |
| WHO | World Health Organization |
| WY | Woman Years |

## DEFINITIONS

| | |
|---|---|
| Adverse Event (AE) | An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. |
| Data cut-off | Includes all data with a date of occurrence up to and including the data cut-off date. |
| Modified Intent-to-Treat (MITT) Population | All subjects between 16 and 35 years of age at study entry for whom the assigned IUS is successfully placed in the uterus and for whom there is at least one assessment of pregnancy status after inserting the IUS. |
| Per-Protocol (PP) Population | A subset of the MITT population excluding subjects with major protocol deviations, to be identified prior to data cut-off. |
| Safety Population | All subjects enrolled who underwent the IUS insertion procedure, regardless of age and outcome. |
| Serious Adverse Event (SAE) | An adverse event that results in any of the following outcomes: death; life-threatening situation (subject is at immediate risk of death); inpatient hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; congenital anomaly/birth defect in the offspring of a subject who received study drug; important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. |

| | |
|---|---|
| Treatment-Emergent AE (TEAE) | AEs occurring during or after attempted IUS insertion and those pre-attempted IUS insertion existing medical conditions that worsened during the study up to the subject's last known IUS date of use or, for subjects who have discontinued, through 30 days after the subject's last known IUS date of use. |

# 1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Medicines360, Protocol M360-L102 [A Phase 3, Multi-Center, Open-Label Study of a Levonorgestrel-Releasing Intrauterine System for Long-Term, Reversible Contraception]. The purpose of this plan is to provide specific guidelines from which the analysis will proceed. Any deviations from these guidelines will be documented in the clinical study report (CSR). In the event where discrepancies in statistical analysis may be encountered between the SAP and what is described in the study protocol, the SAP will take precedence.

# 2. STUDY OBJECTIVES

This study is being performed to evaluate the Medicines360 levonorgestrel-releasing IUS, LNG20. LNG20 is expected to provide safe and effective contraception for up to 10 years.

## 2.1 Primary Objective

The primary objective of this study is to assess the efficacy of a levonorgestrel-releasing intrauterine system (LNG20) in nulliparous and parous females of child-bearing potential who request long-term, reversible contraception.

## 2.2 Secondary Objectives

The secondary objectives of this study are to assess:

- The safety, tolerability, bleeding patterns, and continuation rates of LNG20
- The occurrence of menses and return to fertility after IUS discontinuation
- Plasma pharmacokinetics of levonorgestrel in a subset of approximately 60 subjects with serial sampling over the duration of use
- Plasma levonorgestrel levels in a subset of 60 subjects (LNG20 16 – 35 years old arm only) following IUS removal at 121 months with sampling at various time points up to 14 days post-IUS removal
- Levonorgestrel plasma levels will be obtained for all subjects at each study visit beginning with Month 36 until Protocol Version 9 when thereafter, levonorgestrel plasma levels will be obtained in all subjects at discontinuation and also annually in all women enrolled prior to 31May2011.
- Analysis of an appropriate sampling of IUSs that are removed and, when available, expelled during the study

- The safety and tolerability of LNG20 in a small cohort of women between ages 36 and 45 years up to 8 years of use
- Endometrial thickness in a subset of 60 LNG20 16-35 year old subjects at 1 year, 5 years and 10 years

## 3. STUDY DESIGN AND PLAN

This is a Phase 3, open-label, multicenter evaluation of the efficacy of a levonorgestrel-releasing intrauterine system (LNG20). The original study design included a comparator group of a marketed levonorgestrel-releasing intrauterine system (Mirena) to provide comparative safety and tolerability data for European regulatory approval. The study design changed such that the Mirena group would no longer be needed for comparison; hence the recruitment of the Mirena group was terminated with 159 subjects enrolled. The data from these subjects will be used as an informative comparator only in summary demographic, medical history, adverse event incidence, vital signs, and laboratory results tables given the final Mirena group sample size.

The goals of the study include provision of information to understand efficacy and safety within the widest range of possible users of the LNG20. Typically, intrauterine contraceptive studies only include women 18-35 years of age for efficacy and safety, and place limits on parity and larger body size. Women outside of these characteristics also desire an effective intrauterine contraceptive. Accordingly, this study will include women who are both nulliparous and parous as well as women less than 18 years of age in the primary efficacy and safety analyses. Additionally, we will provide safety information on women greater than 35 years of age. Also, this study does not restrict enrollment based on weight or BMI.

Eligible subjects for the efficacy evaluation of LNG20 will include a minimum of approximately 1600 subjects 16-35 years of age using LNG20. In the original protocol, approximately 650 LNG20 and 160 Mirena subjects were randomized at a 4:1 ratio of LNG20 to Mirena. In the amended single-arm protocol currently in force, the remaining approximately 950 subjects will be assigned to LNG20 only. The 1600 LNG20 subject total represents the combined LNG20 exposure in women aged 16-35 under protocol versions 1.0 through 4.0 using the original inserter and protocol versions 5.0 and later utilizing the redesigned LNG20 inserter. Subjects in the Treatment PK substudy (approximately 60) will be assigned by the IVRS separately from the remainder of study subjects based on BMI. An additional 150 eligible females 36-45 years of age will receive LNG20 as part of a non-randomized cohort to provide additional safety and tolerability information, since IUSs are used with relative frequency by women over the age of 35.

Subjects who discontinue treatment for any reason will not be replaced.
After consent is obtained, screening procedures will be performed and eligible subjects enrolled into the trial via an Interactive Voice Response System (IVRS). Enrollment and IUS insertion may occur on the same day as the screening procedures. The assigned IUS will be inserted by a study Investigator using standardized procedures specific to each system.

LNG20 subjects will be evaluated during study treatment use for up to 85 months (Mirena subjects for up to 60 months). Study assessments will be performed at a clinic visit at Screening/Enrollment and Months 1, 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114, 120 and 121 (Mirena subjects only through Month 60 and LNG20 36-45 years old subjects only through Month 96). Telephone assessments will occur at 3 month intervals between scheduled study visits, starting at Month 9. The IUS will be removed when requested by the subject, when clinically indicated, when requested by investigator or sponsor, or at the end of 121 months of use (60 months for Mirena subjects and 96 months for LNG20 36-45 years old group).

All subjects will have a follow-up safety visit one month after discontinuing the study treatment. Additional follow-up will be conducted for subjects who:

- Have an ongoing IUS or IUS procedure-related adverse event
- Choose a non-hormonal contraceptive method or who indicate that they will attempt to become pregnant, as follows:
    - Those women who elect to start a non-hormonal contraceptive method or no contraception (including those desiring pregnancy) will be followed for return of menses or until diagnosis of secondary amenorrhea is determined
    - Those women who desire pregnancy will be followed for up to 12 months to document return to fertility

Pregnancies that occur during study treatment or after IUS discontinuation through the 30-Day Safety Follow-up Visit will be identified through subject query and urine and serum pregnancy testing. The date of conception will be confirmed by ultrasound examination for pregnancies that occur during study participation. All pregnancies with a date of conception "on treatment" (while the IUS remains in place or up to and including 7 days following IUS discontinuation) will be followed to completion and the outcome recorded.

Routine safety monitoring (including clinically indicated physical exams, adverse event assessments, and vital signs) will be conducted for all subjects. An Independent Data Monitoring Committee (IDMC) will monitor subject safety throughout study conduct, and will be sent reports of all unexpected related serious adverse events (SAEs) that may occur during the study. The IDMC will review all safety data and pregnancy rates, and make recommendations regarding study conduct.

Subjects will receive detailed instructions on how to record vaginal bleeding, dysmenorrhea, and other contraceptive use on a daily diary during the first 24 months of study participation. Thereafter, only other contraceptive use will continue to be recorded daily on a diary for the remainder of study treatment in addition to the information collected at each study visit. After 24 months, bleeding and dysmenorrhea information will be obtained for the remainder of study treatment via interviews by study staff during each study follow-up visit and contact (every 3 months) during treatment.

In addition, levonorgestrel plasma levels will be obtained for all subjects every 6 months and at IUS discontinuation beginning with Month 36 until Protocol Version 9 when thereafter, levonorgestrel plasma levels will be obtained in all subjects at IUS discontinuation and also annually in all women enrolled prior to 31May2011.

The Sponsor intends to retain all IUSs that are removed or expelled (when possible) and analyze an appropriate sample of these systems.

The following substudies will be performed at selected sites:

- Levonorgestrel PK data will be obtained in a subset of approximately 60 subjects (20 non-obese LNG20 subjects, 20 non-obese Mirena subjects and 20 obese LNG20 subjects). LNG plasma samples will be obtained at Enrollment (pre-IUS insertion), Weeks 1 and 2, and Months 1, 3, 6, 9, 12, 18, 24, 30 or Early Discontinuation after IUS insertion (includes three extra visits at Weeks 1 and 2, and Month 9, not included in the main study). These subjects will be required to give informed consent for participation in the levonorgestrel PK subset
- A subset of 60 subjects assigned to LNG20 and completing 121 months of study treatment will have levonorgestrel samples obtained at various time points after IUS removal to characterize the LNG elimination profile. Each subject in this subset will be randomized to one time point (one extra visit) post-IUS removal (24 hours, 48 hours, 7 days or 14 days) such that fifteen subjects are randomized to each time point

- A subset of 60 women assigned to LNG20 at selected sites will have transvaginal ultrasound evaluations at enrollment (pre-IUS insertion), one year, five years and ten years (pre-IUS removal) to assess changes in endometrial thickness

## 4. DETERMINATION OF SAMPLE SIZE

Sample size was determined to achieve an acceptable Pearl Index through a minimum of 10 years of use. Eligible subjects 16-35 years of age will include approximately 1,600 subjects using LNG20 and 160 subjects using Mirena. In the original study protocol, approximately 650 LNG20 and 160 Mirena subjects were randomized in a 4:1 ratio of LNG20 to Mirena. However, under the amended single-arm protocol currently in force (version 5.0 or later), the remaining 950 subjects will be assigned to LNG20 only. Estimation of the required number of subjects needed to evaluate the contraceptive efficacy of LNG20 is based on the Pearl Index, defined as the estimated rate of pregnancy per 100 women per year based on thirteen 28-day cycles of exposure per year. For this study, the following assumptions have been made regarding the Pearl Index:

- It is estimated to be less than 0.280
- The difference between the point estimate and the upper limit of the 95% confidence interval of the Pearl Index calculated for each year of use will be no larger than 1 unit (Benda et al, 2004; Gerlinger et al, 2003)
- Early discontinuations due to dropouts, IUS expulsions, pregnancies and other reasons will not exceed 20% in year 1, 19% per year in year 2, 17% in year 3, and 16% per year in year 4, year 5, year 6, year 7, year 8, year 9 and year 10, and will result in a cumulative discontinuation over 10 years of 76%
- Loss of women-months for use in calculating the Pearl Index will not exceed 0.6 months per subject in year 1 and 0.3 months per year in years 2, 3, 4, 5, 6, 7, 8, 9 and 10

With these assumptions, it is expected that, for the efficacy analysis, 1,600 LNG20 subjects (16-35 years old) will provide at least 10,000 woman-months (28-day cycles) of exposure in the first two years with at least 200 subjects having at least two years of LNG20 exposure within that total 28-day cycle calculation. In addition, the planned sample size assumes that at least 375 women will still be on treatment through the end of ten years. For the purposes of calculating the Pearl Index, a minimum of 200 women must complete each year of study.

# 5. GENERAL ANALYSIS CONSIDERATIONS

## 5.1 Data Summaries

Summary tables, figures, and data listings will be used to report the efficacy and safety outcomes for this study. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. No formal statistical testing of any kind will be performed for this study.

Efficacy summaries consisting of the Pearl Index point estimate and its 95% confidence interval will be limited to the LNG20 16-35 year old study population, and the principal calculation based on all 28-day cycles of use where no other birth control method was reported. Subgroup assessments of pregnancy outcomes by *a priori* defined criteria, e.g., BMI, will be presented for the LNG20 16-35 year-old and LNG20 36-45 year-old study populations. Safety summaries will include the LNG20 16-35 year-old, LNG20 36-45 year old, and Mirena study populations. Depending on the safety endpoint of interest, the LNG20 study populations may be presented as a pooled sample of all subjects exposed to LNG20.

Individual subject data obtained from the case report forms (CRFs), pharmacokinetic data, and any derived data will be presented by treatment group and subject in data listings. This will include subject-level data listings by site as described [redacted] that include derived data fields (e.g., estimates for missing adverse event onset dates) will include the original reported data and the derived value.

All forms of output described in this plan or any amendment that follows prior to any database cut-off for analyses or final database lock are considered *a priori* considerations. Any analyses performed subsequent to database cut-off or final database lock will be considered post-hoc and exploratory. Post-hoc analyses will be identified in the CSR.

All analyses and tabulations will be performed using SAS® Version 9.3 or higher. Pharmacokinetic analyses will be performed using Phoenix® WinNonlin® Version 6.4. Tables, figures, and listings will be presented in RTF/DOC (MS Word-readable) format. Upon completion, all SAS programs will be validated by an independent programmer. In addition, all program output will undergo a senior level statistical review. The validation process will be used to confirm that statistically valid methods have been implemented and that all data manipulations and calculations are accurate. Checks will be made to

ensure accuracy, consistency with this plan, consistency within tables, and consistency between tables and corresponding data listings. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

## 5.2 Data Handling

### 5.2.1 Conventions

Percentages will be based on available data, and denominators will generally exclude missing values.

The precision of the original measurements will be maintained in summaries and listings, when possible. Generally, means, medians and standard deviations will be presented with an increased level of precision as follows: means and medians will be presented to one more decimal place than the raw data, and the standard deviations will be presented to two more decimal places than the raw data.

Summaries of continuous variables that have some values recorded using approximate values (e.g. < or >) will use imputed values. The approximate values will be imputed using the closest exact value for that measurement. Listings will present the data in the original format.

For tables where rounding is required, rounding will be done to the nearest round-off unit. For example, if the round-off unit is the ones place (i.e., integers), values >= XX.5 will be rounded up to XX+1 while values < XX.5 will be rounded down to XX.

For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to “lost to follow-up,” this reason will be included in the table with a count of 0. Categories with zero counts will not have zero percentages displayed.

### 5.2.2 Unscheduled Visits

Unscheduled visits will be used in the determination of baseline value when applicable, but will otherwise only be listed in the applicable data listings.

## 5.3 Handling of Dropouts or Missing Data

Unless otherwise specified, missing data will not be imputed. Subjects who drop out will not be replaced and all available data will be used.

### 5.3.1 Diary Data

Daily diary entries by the subject are made directly onto paper CRFs and are, therefore, "self-sourcing" source data. If a subject does not bring the original (O) diary to the clinic visit, then the site will ask the subject to recall the data on a diary copy (C). The copy will be used until the original is returned at a following clinic visit. During the first 24 months of the study, the diary data for bleeding, cramping and other contraception use will be recorded by the subject on a daily basis. Beginning after month 24, the subject will continue to record other contraception use on a daily diary but bleeding and cramping information will be characterized on a bleeding/cramping form completed by the site through subject interview approximately every 3 months.

If the original diary becomes available after the data from the copy have been entered into the study data base, the data base will be updated to include the original diary data along with the copy. The data base audit trail will reflect initial data entry from the copy followed by subsequent entry of the original. Diaries returned by the subject that include days when no information was obtained have those data records included in the data base. However, no such blank records are in the data base for entire diary pages that may have not been returned, e.g., the subject may have returned diaries for March and May but never returned the April diary. In these cases, missing data are not part of the data base but are accounted for as blank records in the same manner as those which appear, essentially at random, within a returned diary. Since the diary day counting process for identification of 28-day cycles when another birth control method use was reported looks at each diary date record relative to the IUS insertion date, the presence of missing diary records will not affect this calculation. The extent and magnitude of missing diary records will be assessed and presented as part of overall diary results.

Diary numbers on CRFs will not be used; only the date information on the CRF will be used. If the date recorded does not exist, the data will not be included. If the subject never returns the original copy, the copy will be used for analyses. Duplicate diary records (e.g., an original and a clinic copy) for the same study day can appear in the study data base and should be handled as follows:

- If the diaries represent an original diary and a clinic copy diary, the original diary data will serve as the diary data of record.
- If the diaries are submitted as duplicates of the same original or same clinic copy, the most recently submitted version will be used for analyses.

Bleeding and cramping categories are listed below in order of increasing severity.

- Bleeding: None, Spotting, Light Flow, Normal Flow, Heavy Flow.

- Cramping: None, Mild, Moderate, Severe.

*Note: In an early version of the diary, this information was recorded as None, Spotting, or Bleeding. In the analysis, if the subject did not complete a revised diary, the category of "bleeding" will be considered "Normal Flow."*

### 5.3.2 Bleeding, Cramping, and Other Contraceptive Use

For the categories of bleeding, cramping and other contraception use, no imputation of data from the diaries will be done for missing data. For example, a subject with completely missing data for a particular diary day will be considered as having no reported bleeding, no cramping, no other contraceptive use, etc. for that day. Missing data for, say, bleeding alone will be considered as the subject having no reported bleeding for that day.

### 5.3.3 Missing Adverse Event Start and Stop Dates

For adverse events (AE), the following rules for imputing values for missing start dates are used:

- If the AE start date field includes a SAS missing value (e.g., .N) or is completely missing, the start date is set to the IUS insertion attempt date. This conservatively assumes that the AE began on the same date when insertion was first attempted.
- If the AE start date field is missing day only, set it equal to the first day of the recorded month and year.
- If the AE start date field is missing day and month only, set it equal to the first day of January of the recorded year.
- Any resultant imputed AE start date that is earlier than the IUS insertion attempt date is set equal to the IUS insertion attempt date. This also conservatively assigns the AE as having occurred on the same date as the IUS insertion attempt.
- If the AE stop date is completely missing, the event will be noted as "Continuing" in the stop date column in the AE listings.
- If the AE stop date field is missing day only, set it equal to the 15th day of the recorded month and year
- If the AE stop date field is missing day and month only, set it equal to the 31st day of December of the recorded year.

- If the AE stop date field is missing month only, set it equal to December of the recorded year.
- A resultant imputed AE stop date that is earlier than the AE start date is set equal to the AE start date. This ensures that that all AEs have a minimum duration of one day.

### 5.3.4 Missing Concomitant Medication Start and Stop Dates

For concomitant medications (CM), the following rules for imputing values for missing start dates are used:

- If the CM start date field includes a SAS missing value or is completely missing, the start date is set to the IUS insertion attempt date.
- If the CM start date field is missing day only, set it equal to the first day of the recorded month and year.
- If the CM start date field is missing day and month only, set it equal to the first day of January of the recorded year.
- If the CM stop date field includes a SAS missing value or is completely missing, the stop date is set to the last date of known product use.
- If the CM stop date field is missing day only, set it equal to the 15th day of the recorded month and year
- If the CM stop date field is missing day and month only, set it equal to the 31st day of December of the recorded year.
- If the CM stop date field is missing month only, set it equal to December of the recorded year
- Any imputed CM stop date that is before the insertion attempt date implies the CM was a Pre-Trial Medication. Any medication started on or after the insertion attempt date or any medication started before insertion but ending on or before the last known date of product use is a Concomitant Medication.

### 5.3.5 Missing Dates for Other Events, Including Return to Menses, Return to Fertility, Pap Tests, Date of IUS Expulsion/Removal, and Reported Pregnancies

For missing dates of other events, any date that is completely missing or contains the year only will be set to the date of the subject's last clinic visit. If a month and year are recorded but the day is unknown, the day will be set to the first day of the month. If this

results in an imputed date that is earlier than the last clinic visit, the date will be set to the date of the last clinic visit.

## 5.4 Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- **Study day** – For a given date (*date*) on or after successful IUS insertion (*iusindt*), study day is calculated as:

  Study day = date – iusindt + 1

  For a given date (*date*) prior to successful IUS insertion (*iusindt*) or for subjects with failed insertion, study day is calculated as:

  Study day = date – iusindt.

  The day of successful IUS insertion is Study Day 1 and the day prior to IUS insertion is Study Day -1. There is no Study Day 0

  **Months** – A duration expressed in months is calculated as the number of completed calendar months plus the proportion of any partial month completed A month is calculated using the following formula: Dura**t**ion in months = (date2-date1)/30.4
- **Years** - A duration expressed in years between one date (*date1*) and another later date (*date2*) is calculated using the formula noted below:

  Duration in years = (date2-date1)/365.25
- **Age** - Age is calculated as the number of years from the date of birth (*DOB*) to the IUS insertion attempt date (iusindt). For displaying a subject's age, the following formula is used:

  Age (years) = floor (insertion attempt date - birthdate)/365.25
- **Body Mass Index (BMI)** - BMI is calculated using height (in cm) and weight (in kg):

  BMI (kg/ $m^2$) = weight (kg) / [[height (cm)/100]$^2$]
- **Cycles of Use/**– Cycles are calculated using the date the IUS was expelled/removed (from the IUS Discontinuation CRF). Total use duration expressed as the number of 28-day cycles is defined as (IUS expulsion/removal date - date of IUS insertion (*iusindt*)+1)/28. If the expulsion/removal date is unknown then:
    - Subjects who are still on treatment will have their last known date of product use used in the cycle calculations in lieu of an IUS expulsion/removal date, derived as follows: For the evaluation of safety, the last known date of product use will be the last date of on-study contact with the subject where she reported that the IUS is still in place or the last date at which a pregnancy

test was performed (at study site or outside laboratory with copy of report), whichever is later. For the evaluation of efficacy, the last date at which a pregnancy test was performed will be used (at study site or outside laboratory with copy of report).

- If, during on-study contact with the subject (e.g., Month 9 Contact, Month 15 Contact, Month 21 Contact), she reports that the IUS is no longer in place, the date of contact minus 1 day or last date at which a pregnancy test was performed (at study site or outside laboratory with copy of report), whichever is later, will be used as the last date associated with IUS use.
- Subjects who become pregnant with the IUS still in place will have their estimated date of conception used as the last IUS use date.
- In the cases of subjects who are lost to follow-up or withdraw consent prior to IUS removal and neither a last contact date nor a last pregnancy test date is available, the IUS insertion date + 1 day will be used as the last date associated with IUS use.

Similarly, for subjects who had a successful IUS insertion but who have not yet had any post-insertion data (e.g., diaries or post-insertion pregnancy test results) retrieved at the site which could be used to directly calculate duration of use, the IUS insertion date +1 day will be used as the last date of IUS use for the purpose of analysis. For the summary of duration of product use, all subjects with ≥ 1 days of product use, as defined in this section, will be included in the calculations. For the evaluation of adverse events, subjects with less than one calculated complete 28-day cycle of use (at least 23 days) will be excluded unless such subjects reported an adverse event at any time during the first 28 days following IUS insertion (see Section 11.2: Adverse Events for more detail).

## 5.5 28-Day Cycles of Use Calculation for Efficacy Evaluation

In addition to the calculation of 28-day cycles based on last date of IUS use as described in Section 5.4, the efficacy evaluation requires the exclusion of cycles from the Pearl Index denominator where the use of other birth control methods was reported. Since this information is obtained exclusively from subject daily diaries, 28-day cycles of use need to be calculated from the diary data so as to able to determine when the use of other birth control methods occurred.

Using the same algorithm described in Section 5.4, each recorded diary date between the IUS insertion date and the last calculated date of product use, inclusively, is compared to the IUS insertion date in order to calculate cycle number and day. Duration of use expressed as the number of 28-day cycles is then calculated as the maximum duration

(ceiling value) between the IUS insertion date and last recorded diary date. The number of cycles where other birth control methods were used can be calculated directly since each recorded diary record is associated with a cycle number and day.

If the last cycle obtained using either the method described in Section 5.4 or the diary-based method described here has fewer than 23 days, that cycle is considered incomplete and is excluded from the counting process of the number of complete 28-day cycles (see Section 9.2: Primary Efficacy Variable for additional discussion). In addition, if the cycle counts obtained using the method described in Section 5.4 and this section result in different estimates for the number of completed cycles (usually because a subject has stopped completing the diary short of her last site visit or pregnancy test), the smaller of the two calculations will be used. This is a conservative approach that preserves the integrity of the available data as the basis of cycle derivation.

## 5.6 Multiple Comparison/Multiplicity

Since no formal statistical tests are planned for this study, there are no provisions for multiple comparisons or multiplicity adjustment of study endpoints. The Pearl Index point estimate calculations for each of Years 1 through 10 will include 95% confidence intervals that assume an unadjusted two-sided $\alpha$=0.05. This is consistent with the manner in which the Pearl Index is derived in contraceptive efficacy studies. That is, the 95% confidence interval calculation is used as a tool in determining whether the extent of exposure in a given study is adequate to support the precision of the reported Pearl Index point estimate. Note that the Pearl Index will be calculated both on the cumulative year-by-year data and for each year (Years 1 through 10) non-cumulatively.

## 5.7 Interim Analysis and Data Monitoring

### 5.6.1 Interim Analyses

Interim analyses will not be conducted for this study. Sequential supplements to the NDA are planned on a rolling basis beginning after the initial filing and are not considered interim analyses.

### 5.6.2 Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will monitor subject safety throughout study conduct, and will be sent reports of all unexpected related serious adverse events (SAEs) that may occur during the study. The IDMC will review all safety data and pregnancy rates, and make recommendations regarding study conduct. Meetings will occur approximately every six months.

### 5.8 Multicenter Studies

Given that the principal efficacy measure, the Pearl Index, is computed across the combined data across all participating sites, no by-site evaluation or statistical adjustment for site-to-site variation is planned. Summary presentations by site may be considered for specific descriptive variables, e.g., demographic factors, on a by-site basis if warranted.

[redacted]

### 5.9 Subgroup Analyses

Relevant efficacy and safety summaries will be repeated for the following subgroups, using the primary analysis population:

- Age (completed years): < 18, 18 – 30, 31 – 35
- Parity: nulliparous vs. parous
- Race: White vs. Non-white
- Body Mass Index (BMI; kg/m$^2$ round to one decimal place): ≤ 24.9, 25.0 – 29.9, 30.0 – 39.9, ≥ 40
- LNG20 inserter: original (protocol versions 1.0-4.0) vs. redesigned (protocol versions 5.0, 6.0, 7.0, 8.0, 9.0)

The Pearl Index will not be calculated within each of these subgroups; instead, crude efficacy rates will be presented. The Pearl Index calculation becomes less meaningful and difficult to interpret in this situation as the number of available cycles for the exposure denominator necessarily and rapidly diminishes. Also, because these calculated rates rely on the number of subjects as the denominator, individual 28-day cycles of use where other contraceptive methods have been reported will not be considered for exclusion.

## 6. ANALYSIS POPULATIONS

The Safety population will include all subjects enrolled who underwent the IUS insertion procedure, regardless of age and outcome. Treatment assignment will be based on the treatment actually received.

The following subject populations will be used for efficacy analyses:

- Modified Intent-to-Treat (MITT) population will include all subjects between 16 and 35 years of age at study entry for whom the assigned IUS is successfully

placed in the uterus and for whom there is at least one assessment of pregnancy status after inserting the IUS.

- Per-Protocol (PP) population will include subjects in the MITT population with no major protocol deviations (to be identified prior to database cut-off).

The Treatment Pharmacokinetics (PK) population will include all subjects enrolled in the substudy and have at least one post-insertion PK assessment and no major protocol deviations.

The Elimination PK population will include all subjects enrolled in the substudy (who will be randomized to one time point post-IUS removal) and whose post-IUS removal PK assessment is not missing. The elimination PK sampling will only be obtained at the full intended duration of use IUS removal visit (i.e. Month 121).

The Endometrial Thickness (ET) population will include all subjects enrolled in the ET substudy and have at least one post-insertion ET measurement. The final endometrial thickness measurements will be obtained at baseline, Month 12, Month 60 and after the full intended duration of use (i.e. 10 years).

# 7. STUDY POPULATION SUMMARIES

## 7.1 Subject Disposition

Subject disposition information will be summarized for all subjects, by treatment group and by site. Summaries will include: the number of enrolled subjects, the number of subjects with successful IUS insertion (first and second attempt), the number of subjects who discontinued after failed insertion, the number of subjects in each analysis population, the number of subjects completing each visit and the study, and the primary reason for discontinuation.

## 7.2 Protocol Deviations

Major protocol deviations that could potentially affect the primary protocol outcome (efficacy) will be identified prior to database cut-off.

## 7.3 Demographic and Baseline Characteristics

Demographic variables include: age, sex, ethnicity, and race. Other baseline characteristics include: marital status, partner status, height, weight, BMI, medical history, gynecological history, menstrual history, and pregnancy history. General

menstrual history, menstrual history on hormones in the last three months and without hormones in the last three months will be summarized.

Demographic and baseline characteristics will be summarized for the Safety, MITT, Treatment PK, Elimination PK, and ET populations. If the MITT and PP populations are not equivalent, the demographic and baseline characteristics will be summarized for the PP population as well.

# 8. TREATMENT AND MEDICATION

## 8.1 Pre-trial and Concomitant Medications

Verbatim terms on eCRFs will be mapped to the narrowest Anatomical/Therapeutic/Chemical (ATC) class possible and generic drug names using the World Health Organization (WHO) Drug Dictionary Enhanced (DDE). For example, if the 4th level is not available, then the 3rd level (pharmacological subgroup) will be provided.

Concomitant medications include any medication or health product (any prescription medications or over-the-counter preparations) taken during the active study treatment period. Pre-trial medications include any medications taken within seven days (30 days for anticoagulants) of enrollment. Concomitant medications will be summarized for each treatment group by WHO ATC class and generic drug name. These summaries will present the number and percentage of subjects using each medication. Subjects may have more than one medication per ATC class and Generic Drug Name. At each level of subject summarization, a subject is counted once if she reported one or more medications at that level. Each summary will be ordered by descending order of incidence of ATC class and generic drug name within each ATC class.

## 8.2 Extent of Exposure

The number of women-months (28-day cycles) and women-years of exposure will be summarized by treatment group. Exposure to study IUS will be summarized using treatment duration in months both by treatment group and combined across LNG20 treatment groups (16-35 y.o. and 36-45 y.o).

# 9. EFFICACY ANALYSES

The primary efficacy analysis will be based on the MITT population. Additional supportive efficacy analyses will be performed using the PP population, unless the populations are equivalent, as well as the Safety Population.

## 9.1 Pregnancy on Study

For all pregnancy analyses, pregnancy is defined as occurring when a positive urine or blood pregnancy test is reported. Confirmation of pregnancy should be attempted by the study site and may include:

- urine pregnancy test at the study site
- serum quantitative hCG (at study site or report)
- ultrasound examination confirming a pregnancy (at study site or report)
- a surgical procedure for treatment of an extrauterine pregnancy or intrauterine pregnancy (report)

A pregnancy is considered to have occurred "on treatment" if a test or examination confirms a pregnancy and with a date of conception while the IUS is being used as a method of contraception by the subject up to and including 7 days after IUS discontinuation. Pregnancies solely reported by the subject that cannot be verified by any means of examination or follow-up reporting will be evaluated for determination of whether they should be classified as "on treatment" or "not on treatment" for the MITT and PP efficacy evaluations. All reported pregnancies, even if not confirmed by the site, will have a Pregnancy Narrative completed by the study investigator.

## 9.2 Primary Efficacy Variable

The primary efficacy variable is the Pearl Index, an estimation of the number of unintended pregnancies per 100 women-years of exposure. The Pearl Index is calculated as the number of "on treatment" pregnancies in the study divided by the total number of complete 28-day cycles of use (as defined in Section 5.5) in the study across all participating subjects, that result multiplied by 1300 (13 cycles x 100 years). In the case of subjects who are still on study at the time of a Pearl Index calculation, the last known date of product use (defined in Section 5.4) will be used in place of the IUS discontinuation date. A “last cycle” computed using this algorithm will be considered complete if it is at least 23 days in length. In addition, subjects who become pregnant will have that last cycle counted as completed for the Pearl Index calculation, regardless of length.

For the primary Pearl Index outcome using exposure information through Year 5, the MITT population will be used as the basis of exposure and all 28-day cycles where use of another birth control method was reported in the daily diary will be excluded from the total cycle count denominator. Diary days when no information regarding the use other birth control methods is reported will be considered days when no other birth control method use took place. The Pearl Index will be calculated using both the cumulative data

through Year 10 and as individual, non-cumulative year-by-year estimates (see Section 10.1).

For the definitive assessment of contraceptive efficacy, the Pearl Index and its 95% confidence interval will be considered the primary result for inferences.

### 9.3 Secondary Efficacy Variables

In addition to the primary Pearl Index efficacy analysis in the MITT population, the Pearl Index will also be calculated as secondary efficacy variables as follows:

- MITT with no cycle exclusions
  This calculation will include all "on treatment" pregnancies in the numerator and all cycles of use in the denominator. No cycles will be excluded from the denominator.
- The PP study population: The MITT with no cycle exclusions but excluding those subjects with major protocol deviations. Note that use of other birth control methods, by itself, does not constitute a subject being excluded from the PP population.
- LNG20 subjects 36-45 years old, excluding all 28-day cycles where use of another birth control method was reported in the daily diary. Interpretation of the Pearl Index estimate for this subgroup will require caution since the available number of subjects and 28-day cycles of product use will be small and limiting.
- Safety Population: LNG20 subjects 16-45 years old, excluding all 28-day cycles where use of another birth control method was reported in the daily diary
- Sub-group analysis by parity, BMI and race
- Ectopic pregnancies only

"On treatment" pregnancy rate and its associated 95% confidence interval will also be estimated using life table methods with year of use serving as the principal life-table classification.

Life Table analysis will be conducted on the following populations:

- MITT with cycle exclusions
- MITT with no cycle exclusions
- PP
- LNG20 subjects 36-45 years old with cycle exclusions

- LNG20 subjects 36-45 years old with no cycle exclusions
- Safety Population: LNG20 subjects 16-45 years old
- Sub-group analysis by parity, BMI and race
- Ectopic pregnancies only

The life table evaluation with cycle exclusions adjusts for cycles where another birth control method was used. Specifically, it will incorporate the calculation of an "absolute time"-based duration of use that adjusts for cycles where use of another BCM was reported. Duration of use would be based on the total number of 28-day cycles of exposure adjusted downward to account for those cycles where other BCM use was reported, the result converted into years of product use by multiplying by 28 (number of days per 28-day cycle) and then dividing by 364 (number of days in a 13 28-cycle year).

### 9.4 Secondary Efficacy Evaluations for Pre-Specified Subgroups

Calculation of crude pregnancy rates, life table evaluation of efficacy and summary of pregnancy outcomes will be performed within each of the subject subgroups defined in Section 5.9 of this SAP. The life table evaluation will include both the unadjusted and cycle-adjusted for other birth control method use algorithms described in Section 9.3. Pearl Index calculations will not be performed within each of these subgroups, per the reasons given in Section 5.9, e.g., the lack of meaningfulness of the Pearl Index when the number of cycles of exposure is reduced as a result of the subgroup breakdown.

## 10. METHODS OF EFFICACY ANALYSIS

### 10.1 Primary Efficacy Analyses

The primary efficacy endpoint is the Pearl Index for LNG20 women 16-35 years old. The Pearl Index and associated 95% confidence interval (CI) will be presented using the MITT population to establish efficacy for two years of use. Acceptable precision of the Pearl Index is expected to establish efficacy of LNG20 where acceptable precision is typically defined as the upper bound of the 95% CI being no more than 1 unit greater than the point estimate of the Pearl Index.

Since the number of cycles of exposure during the first year is the lowest, this precision of the Pearl Index may not be fully observable if limited to the first year alone. Therefore, while a Pearl Index estimate at year 1 and its 95% confidence interval will be obtained using the available exposure information for year 1 alone, the upper bound of the

confidence interval associated with that estimate may be wider than the "no greater than 1 unit" criterion for years 2, 3, 4, 5, 6, 7, 8, 9 and 10. The Pearl Index for primary efficacy will therefore be calculated as cumulative and also non-cumulative year-by-year.

## 10.2 Secondary Efficacy Analyses

### 10.2.1 Pearl Indices

The cumulative Pearl Index analyses described above for the primary efficacy analysis will also be performed every year after Year 2. The analysis at Years 3, 4, 5, 6, 7, 8, 9 and 10 will only be completed if the efficacy of LNG20 for the preceding years of use meets acceptable precision, where acceptable precision is defined as the upper bound of the 95% confidence interval being no more than 1 unit greater than the point estimate of the Pearl Index. Pearl Index calculations will be done when a minimum of 200 women complete each subsequent year of the study.

### 10.2.2 Pregnancy Rates

Life table methods will be used to estimate the overall pregnancy rate for each year and the cumulative pregnancy rate after each year. Both uterine and ectopic pregnancies will be included. Pregnancy dating and confirmation will be determined by medical assessments, including ultrasound examination. Confirmed pregnancy is the failure outcome and the corresponding time to pregnancy is the failure time. Time to pregnancy will be calculated as the date of conception minus the date of IUS insertion plus one (partial or completely missing conception dates handled per Section 5.3.5). Subjects who do not get pregnant will be censored at the last pregnancy assessment and failure time will be calculated as the date of the last pregnancy assessment minus the date of IUS insertion plus one.

Additionally, an overall Ectopic Pregnancy (EP) rate will be calculated as EP Rate per 100 Woman Years (WY) for the duration of use:

Number of EPs/WYs (number of 28-day cycles) = x/100 WY. The number of 28-day cycles per subject is not to exceed the duration of use being evaluated.

## 10.3 Pharmacokinetic Analyses

### 10.3.1 Plasma Concentrations during IUS Use

Plasma concentrations before insertion of the IUS, and then at Days 7 and 14, and Months 1, 3, 6, 9, 12 18, 24, 30 during IUS use will be analyzed using the Treatment PK

population. Summaries will be presented for non-obese LNG20, non-obese Mirena, obese LNG20, and total LNG20 subjects. Data listings will be provided for all subjects in the PK population.

The plasma concentrations will be summarized at each time point using descriptive statistics, including geometric means, in tabular format. Plasma concentrations over time will be plotted by treatment group. Plasma concentrations reported as below the level of quantification (BLQ) will be set to zero for the purposes of summarizing and plotting concentrations.

10.3.2 Pharmacokinetic Parameters during IUS Use

For each subject, PK parameters will be determined using a non-compartmental approach. The following PK parameters will be calculated: $C_{ssave}$ (pg/mL) and $AUC_{0\text{-}last}$ (day * pg/mL). For the purpose of the non-compartmental PK analysis, all plasma concentrations below the limit of quantification (BLQ) occurring after the first measurable plasma concentration will be set to zero).

PK parameters will be summarized at each time point using descriptive statistics, including geometric means.

Additionally, analyses of the effects of race and body weight on LNG exposure and exposure-response data for the secondary endpoints of return to menses (RTM), return to fertility (RTF) and endometrial thickness (ET) will be performed.

10.3.3 Elimination PK

PK data will be summarized at each time point using descriptive statistics, including geometric means. Plasma concentrations over the first 14 days following LNG20 removal after 121 months of use will be summarized using the Elimination PK population. For the purpose of this analysis, all plasma concentrations below the limit of quantification occurring after the first measurable plasma concentration will be set to zero.

A population PK type analysis will be also performed.

## 10.4 IUS Analysis Post-Removal

Analysis of an appropriate sampling of IUSs for residual LNG content that are removed or expelled during the study will be summarized and plotted as a function of time of removal/expulsion.

# 11. SAFETY ANALYSIS

All safety analyses will be based on the Safety population.

## 11.1 Pregnancy Outcomes

Pregnancy outcomes will be summarized by treatment group.

## 11.2 Adverse Events

Menstrual bleeding and cramping/pain for the first 24 months are recorded in a daily subject diary and not on the Adverse Events CRF (unless the event is an SAE, results in IUS removal or is not related to the IUS or menstrual condition). The subject daily diary has been designed to collect IUS and menstrual bleeding and cramping AEs following insertion of the study IUS. Menstrual bleeding or cramping/pain would only be entered onto the general AE CRF if:

- Bleeding or cramping/pain meet serious criteria; an SAE report would also have to be submitted (this exception is due to data system requirements)
- Bleeding or cramping/pain result in the IUS being removed (this exception is due to data system requirements)
- Bleeding or cramping/pain is not related to the IUS or a menstrual condition.

After 24 months, menstrual bleeding and cramping/pain are recorded on the Adverse Events CRF. Analyses of cramping/pain and bleeding are described below in section 11.6 .

All adverse event summaries will be restricted to treatment-emergent adverse events (TEAE), defined as AEs occurring during or after attempted IUS insertion and those pre-attempted IUS insertion existing medical conditions that worsened during the study up to the subject's last known IUS date of use or, for subjects who have discontinued, through 30 days after the subject's last known IUS date of use. If an AE cannot be determined as treatment-emergent, it will be counted as such.

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Each adverse event summary will be displayed by treatment group. Summaries that are displayed by system organ class and preferred terms will be ordered by descending order of incidence of system organ class and preferred term within each system organ class. Summaries of the following types will be presented:

- Overall subject summary of AEs, SAEs, and deaths
- Subject incidence of TEAEs and total number of unique TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and highest severity. At each level of subject summarization a subject is classified according to the highest severity if the subject reported one or more events. AEs with missing severity will be considered severe for this summary
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and closest relationship to IUS (Related/Not Related). At each level of subject summarization a subject is classified according to the closest relationship if the subject reported one or more events. Related will be defined as "Related", "Probably Related", or missing. Not related will be defined as "Unlikely Related" or "Not Related"
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and closest relationship to IUS Procedure (Related/Not Related). At each level of subject summarization a subject is classified according to the closest relationship if the subject reported one or more events. Related will be defined as "Related", "Probably Related", or missing. Not related will be defined as "Unlikely Related" or "Not Related"
- Subject incidence of serious TEAEs and total number of unique serious TEAEs by MedDRA system organ class and preferred term

Incidence rates will include in the denominator all subjects in the Safety Population.

Missing Severity or Relationship

Missing severity or relationship to study drug will prompt queries to be sent to the investigators to provide the information. If after query resolution, the information remains missing, the following conventions will be used in summary tables.

- An event with missing severity will be considered Severe.
- An event with missing relationship will be considered related to study drug.

### 11.3 Insertion and Removal Related Bleeding and Cramping/Pain

IUS insertion and removal bleeding and cramping/pain related to IUS insertion and removal will be summarized by treatment group. IUS insertion related bleeding and

cramping/pain are recorded on the IUS Insertion Questionnaire. IUS removal related bleeding and cramping/pain are recorded on the IUS Removal Questionnaire.

Summaries of the following will be presented:

- Bleeding (none, spotting, light bleeding, moderate bleeding, heavy bleeding)
- Cramping/pain (none, mild, moderate, severe)

## 11.4 Menstrual Related Cramping/Pain

### 11.4.1 Up to Month 24

For the first 24 months of the study. A subject will be defined as having menstrual cramping/pain (dysmenorrhea) TEAE if:

- The subject diary question, "Check box if cramping today is worse than when not using hormones" is marked

  AND

- Baseline cramping/pain or dysmenorrhea is the same or worsens from what is indicated on the Menstrual History CRF based on menstrual characteristics when not using hormonal contraception.

If cramping/pain (dysmenorrhea) TEAE is recorded on the Adverse Event CRF and not on the subject diary due to the event being an SAE, results in IUS removal or is not related to the IUS or menstrual condition, the subject will be counted as having a cramping/pain (dysmenorrhea) TEAE. Subject incidence of cramping/pain or dysmenorrhea TEAEs will be described within the overall adverse event incidence summary.

### 11.4.2 After Month 24

For Months 25 through 121, cramping/pain (dysmenorrhea) TEAEs will be recorded only in the Adverse Event CRF and not determined based on daily subject diary responses. During these months there will be no subject diary for menstrual changes and instead a periodic (every 3 months) form characterizing their cramping and dysmenorrhea will be used. Self-reported cramping and dysmenorrhea TEAEs will be recorded on the Adverse Event CRF.

## 11.5 Menstrual Related Bleeding

### 11.5.1 Up to Month 24

For the first 24 months of the study a subject will be defined as having a menstrual Bleeding TEAE if:

- The subject diary question, "Check box if bleeding today is heavier than when not using hormones" is marked

  AND

- Baseline bleeding that is the same or worsens from what is indicated on the Menstrual History CRF based on menstrual characteristics when not using hormonal contraception.

If a bleeding TEAE is recorded on the Adverse Event CRF and not on the subject diary due to the event being an SAE, results in IUS removal or is not related to the IUS or menstrual condition, the subject will be counted as having a bleeding TEAE. Subject incidence of bleeding TEAEs will be described within the overall adverse event incidence summary.

### 11.5.2 After Month 24

For Months 25 through 121, bleeding TEAEs will be recorded only in the Adverse Event CRF and not determined based on daily subject diary responses. During these months there will be no subject diary for menstrual changes and instead a periodic (every 3 months) form characterizing their bleeding will be used. Self-reported bleeding TEAEs will be recorded on the Adverse Event CRF.

## 11.6 Diary Reported Bleeding and Cramping/Pain Analysis

### 11.6.1 Months 1-24

For each 28-day cycle and each 84 and 90 day interval post-insertion, the incidence of on-treatment cramping/pain (none, mild, moderate, severe) and bleeding (none, spotting, light flow, medium flow, heavy flow) will be calculated based on diary entries and presented by treatment group. Summaries of the following types will be presented:

- Incidence of cramping/pain by 28-day cycle and 84 and 90 day intervals post-insertion (none vs. ≥1 day; 1-3, 4-7, >7, and >20 days)

- Incidence by of bleeding by 28-day cycle and 84 and 90 day intervals post-insertion (none vs. spotting vs. bleeding; none vs. ≥1 day; 1-3, 4-7, >7, and >20 days; no bleeding vs. any bleeding)
- Incidence of cramping/pain by highest severity or bleeding by greatest intensity by cycle and 84 and 90 day intervals post-insertion. At each level of subject summarization a subject is classified according to the highest severity or intensity if the subject reported one or more events.

Descriptive continuous-based statistics (mean, standard deviation, median, minimum, maximum) will be used to summarize the number of days of reported cramping and bleeding and/or spotting during each 28-day cycle and each 84 and 90-day interval. The number of spotting days and the number of bleeding days (light flow, moderate flow, heavy flow combined and each category separately) will also be summarized using this approach. For cramping/pain, this will also be presented within each severity rating, i.e., the total number of reported days will be broken down into the number of days of mild, moderate, and severe cramping/pain.

11.6.2 After Month 24

The incidence of reported cramping every three months after Month 24 will be reported using the categories which appear in parentheses below:

- Over the last 3 months has the subject had any menstrual cramping/pain? (Yes/No)
- Did the cramping/pain occur mainly when the subject was having any bleeding or spotting? (Yes/No)
- The worst cramping/pain experienced during these months (mild, moderate, severe)

The incidence of bleeding and/or spotting will be presented in a similar fashion based on the following questions and categories of response:

- Over the last 3 months has the subject had any menstrual bleeding/spotting?
- What was the main pattern of bleeding/spotting the subject experienced for these months? (Just Spotting, Irregular Bleeding, Regular Bleeding [periods])
- The heaviest bleeding experienced for these months (Spotting, Light Flow, Normal Flow, Heavy Flow)

### 11.7 Site Diaries

A Site Diary was originally implemented to characterize subject bleeding and cramping after Month 24. The Site Diary had identical bleeding and cramping questions as the Subject Diary for Months 1-24. The Site Diary was replaced with the Bleeding/Cramping Form. Those subjects for which the Site Diary was completed before the initiation of the Bleeding/Cramping Form will have similar analysis performed as for Months 1-24 for bleeding and cramping pain as outlined in section 11.6.1.

### 11.8 Insertion

All insertion analyses will be presented separately by inserter type, SHI-001 new inserter and original inserter, and combined data for both inserters.

The number and percentage of subjects with a successful insertion and where rigid cervical dilation or local anesthesia was used will be presented by treatment group. The distribution of easy, neutral, or difficult insertions will be summarized by treatment group. The summaries will be presented by insertion attempt.

Summaries will also be presented by inserter type for other inserter-related outcomes, such as the number and percentage of subjects where insertion failure occurred, difficulty of insertion, use of cervical dilation, perforation, expulsion, and insertion-related bleeding and cramping.

Some subjects will be enrolled (assigned in the IVRS) and will meet the protocol defined IUS insertion failure, which is when, after contact with the cervical os by the inserter, completion of IUS insertion is not achieved. However, some of these insertion failures are unrelated to the study IUS or inserter and such cases will not be analyzed as insertion failures. Examples of such situations include, but are not limited to:

- withdrawal of consent after enrollment and before IUS placement
- cervix could not be visualized
- inserter became contaminated
- subject could not tolerate sounding
- uterus could not be sounded
- uterus sounded to < 5.5 cm
- enrolled but determined not to be eligible before IUS placement

- prior IUD in uterus could not be removed.

Subjects who had a failed first insertion but never came back for a second attempt are considered to be a failed insertion and not a discontinuation due to withdrawal of consent or lost to follow-up.

### 11.9 Continuation, Expulsion, and Removal Rates

Cumulative rates of IUS continuation, expulsion, and safety-related removal at 6 months, Years 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 will be summarized. Time to event will be calculated as the date of continuation/expulsion/removal minus the date of IUS insertion plus one. Subjects without a continuation/expulsion/removal will be censored at the last contact date (as described in Section 5.4) and failure time will be calculated as the last contact date minus the date of IUS insertion plus one. Subjects who report an expulsion that is not confirmed by the study site will be censored. The safety-related removal rates may also be summarized by MedDRA preferred term in the same manner.

Expulsion rates including analysis of complete and partial expulsions by inserter type, parity and duration of use (by year) in the Safety Population will also be summarized.

### 11.10 Fertility Rates Post-Removal

Cumulative fertility rates for each month of the first year following IUS removal for women who desire pregnancy or who do not use any contraception and become pregnant, based on the Final Status CRF, will be summarized by treatment group. Time to event will be calculated as the date of pregnancy minus the date of removal plus one. Subjects who do not get pregnant will be censored at 12 months and failure time will be calculated as 12 months date minus the date of removal plus one. Subjects who initially desire to become pregnant after IUS discontinuation but do not complete a full 12 months before discontinuing the effort to achieve pregnancy will be excluded from the analysis.

### 11.11 Return to Menses

The time to return to menses for each month following IUS removal for those women who are using non-hormonal contraceptive methods or no contraception following IUS discontinuation will be summarized by treatment group. Time to event will be calculated as the date of menstruation minus the date of removal plus one. Subjects who do not have a return of menstruation will be censored at the date of diagnosis for secondary amenorrhea and failure time will be calculated as the date of diagnosis for secondary amenorrhea minus the date of removal plus one.

## 11.12 Pelvic and Breast Examinations

Any abnormal pelvic or breast findings will be included in the adverse event reporting.

## 11.13 Clinical Laboratory Evaluation

### 11.13.1 Hemoglobin

Hemoglobin will be summarized using descriptive statistics at Baseline, Month 12, Month 60 and the Final Visit. Final Visit is defined as either the early discontinuation or study treatment completion visit. Baseline is defined as the last non-missing value prior to IUS insertion. However, if a baseline value is not obtained due to protocol deviation or laboratory error, a Month 1 visit or an Unscheduled Visit within the Month 1 visit window will be used as Baseline in a sensitivity analysis. Changes from Baseline at Month 12, Month 60 and the Final Visit will also be summarized.

### 11.13.2 Chlamydia and Gonorrhea Evaluations

The frequency and percentage of Chlamydia and gonorrhea results will be summarized for each applicable visit by treatment group. Similar to hemoglobin analyses, if a baseline value is not obtained due to protocol deviation or laboratory error, a Month 1 visit or an Unscheduled Visit within the Month 1 visit window will be used as Baseline in a sensitivity analysis. In addition, the frequency and percentage of subjects with a change in sexual partners will be summarized.

### 11.13.3 Pap Tests

The frequency and percentage of Pap test results will be summarized for each applicable visit by treatment group.

### 11.13.4 Serum Chemistry and Urine Pregnancy Tests

Serum chemistry and urine pregnancy tests will be listed by treatment group and subject.

## 11.14 Endometrial Thickness

Endometrial thickness at baseline and after 1, 5 and 10 years of LNG20 use will be summarized using the ET population. Changes from baseline will also be summarized. Baseline is defined as the last non-missing value prior IUS insertion.

### 11.15 Vital Signs

Vital signs, blood pressure and weight, will be summarized using descriptive statistics at baseline and at each post-baseline time point. Changes from baseline will also be summarized. Baseline is defined as the last non-missing value prior to IUS insertion. Temperature and height will only be presented in listings.

## 12. REFERENCES

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