Statistical Analysis Plan

Medicines360

Protocol: M360-L105

A Phase 3, Multicenter, Open-Label Study of a Levonorgestrel 52 mg Intrauterine System for the Treatment of Heavy Menstrual Bleeding

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LIST OF ABBREVIATIONS

AE	adverse event
AH	Alkaline hematin
ATC	Anatomical Therapeutic Chemical
BOCF	Baseline observation carried forward
BMI	body mass index
BP	blood pressure
cm	centimeter(s)
CM	Concomitant medication
CRF	case report form
CSR	clinical study report
DDE	drug dictionary enhanced
g	gram(s)
HMB	Heavy menstrual bleeding
in	inch(es)
ITT	Intent-to-Treat
IUS	intrauterine system
kg	kilogram(s)
lb	pound(s)
l	Liter
LNG	Levonorgestrel
LOCF	Last observation carried forward
LTFU	Lost-to-follow-up
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram(s)
mL	Milliliter
MBL	Menstrual blood loss
MITT	Modified Intent-to-Treat
N	Number
Ng	nanogram
PP	Per-Protocol
SAE	serious adverse event

SAP	statistical analysis plan
SAS	SAS® Software
TEAE	treatment-emergent adverse event
WHO	World Health Organization

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.
Amenorrheic (Treatment Cycle 3 and Cycle 6)	No spotting or bleeding with no feminine hygiene product use, or only spotting or light bleeding but no feminine hygiene product use, during the entire 28-day collection interval in either Treatment Phase Cycle 3 or Cycle 6.
Intent-to-Treat (ITT)	All subjects with qualifying baseline data at study entry for whom the IUS is successfully inserted.
Modified Intent-to-Treat (MITT) Population	All subjects with qualifying baseline data at study entry for whom the IUS is successfully inserted and for whom there is at least one assessment of MBL during the Treatment Phase Cycle 3 or Cycle 6. All MBL values reported for both validated and unvalidated used feminine hygiene products will be included.
Supportive MITT	A supportive subset of the MITT population with baseline and post-baseline MBL data reported collected from only validated feminine hygiene products. This population is to demonstrate the robustness of the efficacy analyses.
Per-Protocol (PP) Population	A subset of the MITT population that excludes subjects with major protocol deviations that are determined to have impact on the data of MBL assessment.

Safety Population	All subjects enrolled who had an IUS insertion attempt regardless of 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)	New AEs that occur and existing medical conditions that worsen during the study, beginning from the IUS insertion attempt and ending when the insertion attempt is declared a failure or on the subject's last known IUS date of use or the Safety Contact whichever is later.

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Medicines360, Protocol M360-L105 [A Phase 3, Multicenter, Open-Label Study of a Levonorgestrel 52 mg Intrauterine System for the Treatment of Heavy Menstrual Bleeding]. 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 Statistical Analysis Plan (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 (commercially available in the U.S. as Liletta®). LNG20 IUS is expected to provide safe and effective treatment for heavy menstrual bleeding (HMB).

2.1 Primary Objective

The primary objective of this study is to assess the efficacy of a levonorgestrel 52 mg intrauterine system (LNG20 IUS) as a treatment for heavy menstrual bleeding.

2.2 Secondary Objectives

The secondary objectives of this study are to assess the safety, tolerability, bleeding patterns, and continuation rates of LNG20 IUS in women using LNG20 IUS for heavy menstrual bleeding.

3. STUDY DESIGN AND PLAN

This is a Phase 3, open-label, multicenter evaluation of the efficacy of a levonorgestrel 52 mg intrauterine system (LNG20 IUS) for the treatment of heavy menstrual bleeding.

After completing screening and confirming eligibility, approximately 100 women, 18-50 years of age, will be enrolled to receive LNG20 IUS. This study will not restrict screening or enrollment based on parity, weight or body mass index (BMI). Women who do not require contraception (e.g., not heterosexually active, using permanent contraception) may be included.

Only women who are willing to forgo contraindicated confounding treatments and systemic hormones for the ascribed period prior to the screening, during the Screening Phase and during the Treatment Phase may be enrolled. Women who are heterosexually active must

use appropriate contraceptive methods during the Screening Phase, such as male or female permanent sterilization, be willing to use a barrier method, withdrawal (if has been using as current method prior to screening) or abstinence. No other contraceptive is required during the Treatment Phase, although subjects may choose to do so as long as contraindicated products are not used.

After written consent is obtained, the subject will undergo a Screening Phase to establish eligibility and confirm the diagnosis of HMB. At the initial screening visit (Visit 1) medical history and vital signs including height and weight will be obtained and a gynecologic exam, uterine ultrasound (unless performed within 6 months), endometrial biopsy (unless performed within 6 months), high sensitivity urine pregnancy test, gonorrhea/Chlamydia testing (unless performed in the last 30 days), Pap test (unless had documented result indicating no further follow-up during anticipated study participation) and blood tests to evaluate eligibility criteria will be performed. Women who meet entry criteria at Visit 1, exclusive of pending testing results (e.g., blood tests, endometrial biopsy, Pap test, etc.) will initiate participation in up to 3 more screening visits (Visit 2, Visit 3 and Visit 4) over approximately 90 days to establish the diagnosis of HMB based on menstrual blood loss (MBL) of ≥80 mL/cycle in at least 2 of 3 cycles as assessed by the alkaline hematin (AH) method.

The participant is expected to have an blood sample drawn for AH assay sample within 21 days after the last day of the feminine hygiene collection (last day of menses for Screening and after the 28-Day collection interval for Treatment Phase Cycle 3 and Cycle 6). All collected feminine hygiene products and the AH blood sample will be sent to the analysis lab within a couple of business days of the visit.

The subject will be provided specific brands of feminine hygiene products and trained to complete a daily bleeding diary. Any subject for whom a pending test result from Visit 1 is reported with an exclusionary result will be discontinued from screening (screen failure).

The diagnosis of HMB will be established in the 2-3 cycles of the screening phase.

A Screening Cycle may be repeated under the following conditions:

- If a subject indicates she was unable to collect all used feminine hygiene products during a menses and, in the opinion of the Investigator, the discarded products contained a substantial volume of blood, that cycle collection may be discarded and the cycle collection repeated
- If a subject indicates she used non-study feminine hygiene products and, in the opinion of the Investigator, these products contained a substantial volume of the blood to be assayed, then that cycle collection may be discarded and the cycle collection repeated

- If subject indicates that the first cycle had significantly less bleeding than her usual cycle, then that cycle collection may be discarded and the cycle collection repeated (first cycle only)
- Only one screening cycle may be repeated. Any screening cycle collection that is assayed cannot be repeated

Due to the COVID-19 pandemic local/state public health officials, University or Hospital leadership, and Institutional Review Boards may have required subject contact changes that impacted some study data collection. Starting in March 2020, subjects were allowed up to two consecutive cycle collections to be delayed during the screening phase for the following reasons:

1) A subject is not permitted to have an in person visit because of a health policy implanted by the site related to COVID-19
2) A subject does not feel comfortable coming into the clinic during the pandemic.

The Screening Phase MBL is the MBL averaged over all cycles measured during the Screening Phase. Each Screening Phase visit will include a high sensitivity urine pregnancy test.

Enrollment (Visit 5) will occur when the LNG20 IUS is attempted to be inserted by a study Investigator using standardized procedures and must occur within 45 days of the Screening Phase visit (i.e., Visit 3 or Visit 4) in which eligibility is established. Up to two insertion attempts will be allowed within 30 days. The study IUS will be considered inserted upon successful completion of the insertion process per the instructions for use in the Liletta USPI (Allergan and Medicines360, 2020). Visit 5 will include a high sensitivity urine pregnancy test which will be repeated if a second insertion attempt is required on a separate day. Additionally, gonorrhea/Chlamydia testing will be repeated for any women with a change in sexual partner since last tested, but IUS insertion does not require waiting for the results. The following baseline assessments will occur on the day of the initial insertion attempt and not repeated should a second attempt on a different day be needed: hemoglobin, hematocrit and ferritin testing, and a subjective assessment of menstrual bleeding using a Visual Analog Scale (VAS) questionnaire.

In the Treatment Phase subjects will continue to use only the study provided feminine hygiene products and record their bleeding on a daily diary. Feminine hygiene product collection will be limited to Cycle 3 and Cycle 6 during the Treatment Phase; no repeat collection is permitted. Study assessments will be performed at clinic visits at Treatment Phase Month 1 (Visit 6), and at the end of Cycle 3 (Visit 7) and Cycle 6 (Visit 8). Each visit will include a high sensitivity urine pregnancy test. Ferritin/hematology assessments and a subjective bleeding assessment using a VAS questionnaire will be performed at Visits 7 and 8. The IUS can be removed during the study when requested by the subject or when clinically indicated. At the end of 6 28-day cycles of use, unless medically

contraindicated, study participants may opt to keep the IUS or otherwise it will be removed.

All subjects for whom the IUS was removed will be contacted 7 to 10 days after the study exit visit to assess bleeding and cramping after removal and any IUS-related or IUS procedure-related adverse events. After completion of the Treatment Phase, all subjects with ongoing IUS-related adverse events that are not resolved or stabilized will have monthly contacts or visits, as appropriate, until the event is resolved or stabilized.

Routine safety monitoring (including clinically indicated physical exams, adverse event assessments, and vital signs) will be conducted for all subjects.

4. DETERMINATION OF SAMPLE SIZE

The sample size estimate of 100 subjects is based on results from previous studies with similar endpoints as well as the goal of a lower 95% confidence around the point estimate of the primary outcome with acceptable precision, i.e., being no more than 10% lower than the point estimate. The estimation of the required number of subjects needed to evaluate the efficacy of the LNG20 IUS is based on the following assumptions:

- The expected successful treatment rate is estimated to be 80% or higher
- The lower bound of 95% confidence interval should be within 10% from the point estimate, i.e., 70% or higher to establish the efficacy of LNG20 IUS for the treatment of HMB
- Early discontinuations due to dropouts, IUS expulsions, pregnancies and other reasons will not exceed 15%

A sample size of 80 - 85 subjects completing the Treatment Phase will provide at least 71.2% lower bound of the 95% confidence interval for an expected successful treatment rate of 80% or higher based on normal approximation. Therefore, 100 subjects using LNG20 IUS with an expected dropout rate of 15 - 20% will provide sufficient number of subjects, for the goal of approximately 80 - 85 subjects completing the trial.

Subjects who discontinue treatment for any reason other than a one-time study IUS replacement within two weeks of a complete or partial expulsion will not be replaced.

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 will be performed for this study for the primary and secondary analysis.

The primary outcome measure, the proportion of subjects with successful treatment defined as end of treatment MBL <80 mL and 50% or less than baseline, will be analyzed with 95% confidence interval based on normal approximation. LNG20 IUS efficacy for the treatment of HMB will be established in this study if the lower bound of the 95% confidence interval equals or exceeds 70%.

Individual subject data obtained from the case report forms (CRFs) and any derived data will be presented by subject in data listings. Listings 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. Tables, figures, and listings will be generated in RTF/DOC (MS Word-readable) and presented in PDF 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

Confidence intervals of proportions will be presented in percentage with one decimal point.

Percentages of categorical variables 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 (except MBL) 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.

The MBL reported values such as <10 mL, <5 mL, <2.5 mL etc. are indicators of the total blood volume of assay being BQL (below the quantifiable limit) and will be imputed to half values (e.g., <5 mL will be imputed to 2.5 mL) for baseline cycles as well as post-baseline cycles.

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 to record bleeding/spotting/cramping 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.

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 will 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 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 diary, 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

5.3.2 Bleeding and Cramping

For the categories of bleeding and cramping 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 or cramping 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 Data for MBL

- A MBL assessment by AH may not be collected for Treatment Phase Cycle 3 and Cycle 6 in which a subject reported being amenorrheic (no spotting/bleeding) for the 28-day collection interval on the CRF for AH Menstrual Blood Loss Assessment; in this case the corresponding MBL value will be set to 0 mL. Additionally, the participant may report spotting only or light bleeding on her diaries with no feminine hygiene products used; in this case the corresponding MBL value will be set to 0 mL
- For a Treatment Phase missed Visit 7 (Cycle 3) or missed Visit 8 (Cycle 6), no imputation of MBL from diary data alone will be conducted.
- For the evaluations of MBL, the last observation carried forward (LOCF) method will be used for imputation. If MBL data in Cycle 3 are available but no MBL data in Cycle 6 are available or Cycle 6 is invalid, then MBL data in Cycle 3 will be used as End of Study MBL.
- Additional imputation method(s) might be explored for sensitivity analysis when deemed necessary

5.3.4 Missing Adverse Event Start and Stop Dates

For adverse events (AE), the following rules for imputing values for missing start and stop 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.

5.3.5 Missing Concomitant Medication Start and Stop Dates

For concomitant medications (CM), the following rules for imputing values for missing start dates and stop 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 and the CM is not ongoing, 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.

5.3.6 Missing Dates for Other Events, Including Date of IUS Expulsion/Removal

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) at Screening Visit 1:

  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 or date of Visit 8 - date of

IUS insertion (*iusindt*)+1)/28. If re-insertion for expulsion takes place, the last IUS expulsion/removal date or date of Visit 8 is used. 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 or date of Visit 8, derived as follows: 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
- If, during on-study contact with the subject she reports that the IUS is no longer in place, the date of reported expulsion/removal if known, or if unknown the date of contact minus 1 day, will be used as the last date associated with IUS use.
- In the cases of subjects who are lost to follow-up or withdraw consent prior to Visit 8 and a last contact date is available, the last contact date- date of insertion (insindt)+1)/28 will be used. If not contact date after insertion is available then date of IUS insertion + 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., Visit 6, Visit 7, Visit 8, unscheduled visit) 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.

5.5 28-Day Cycles of Use Calculation

In addition to the calculation of 28-day cycles based on last date of IUS use as 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.

5.6 Multiple Comparison/Multiplicity

Since no formal statistical tests are planned for the primary and secondary analysis except for the subgroup analysis for this study, there are no provisions for multiple comparisons or multiplicity adjustment of study endpoints.

5.7 Interim Analysis and Data Monitoring

Interim analyses will not be conducted for this study.

5.8 Multicenter Studies

Given that the principal efficacy measure, MBL, 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. Site-specific data set information may also be prepared per regulatory inspection.

5.9 Subgroup Analysis

Descriptive summaries of absolute change in the median MBL from baseline to End-of-study will be provided for the following subgroups with no formal statistical testing;

- Age groups 18 to ≤35 and ≥ 36 years of age
- Race/Ethnicity
- BMI <25, 25 to <30, or ≥30

6. ANALYSIS POPULATIONS

The Safety population will include all subjects enrolled who underwent an IUS insertion attempt, regardless of outcome.

The following subject populations will be used for efficacy analyses:

- Modified-Intent-To-Treat (MITT): All subjects with qualifying baseline data at study entry for whom the IUS is successfully inserted and for whom there is at least one assessment of MBL during the Treatment Phase Cycle 3 or Cycle 6. All MBL values reported for both validated and unvalidated used feminine hygiene products will be included. This is the main population for the efficacy analyses.
- Supportive MITT: A supportive subset of the MITT population with baseline and post-baseline MBL data reported collected from only validated feminine hygiene products. This population is to demonstrate the robustness of the efficacy analyses.
- Per Protocol (PP): A subset of the MITT population that excludes subjects with major protocol deviations that are determined to have impact on the data of MBL assessment.

- Intent-to-Treat (ITT): All subjects with qualifying baseline data at study entry for whom the IUS is successfully inserted. This population is for evaluation of the sensitivity of results obtained from the MITT-based assessments. The baseline MBL will be carried forward (BOCF) for subjects who provide no Treatment Cycle 3 and no Treatment Cycle 6 data.
- Intent-to-Treat (ITT) Excluding Subjects LTFU and Subjects Who Withdrew Consent (WC) Without Study IUS Removal: All subjects with qualifying baseline data at study entry for whom the IUS is successfully inserted, excluding subjects who were LTFU or withdrew consent without study IUS removal and had no MBL assessment after baseline at Treatment Cycle 3 and Cycle 6. The baseline MBL will be carried forward (BOCF) for subjects who provide no Treatment Cycle 3 and no Treatment Cycle 6 data except for those subjects who were LTFU or withdrew consent without study IUS removal. This population is for evaluation of the sensitivity of results obtained from the MITT-based assessments.

7. STUDY POPULATION SUMMARIES

7.1 Subject Disposition

Subject disposition information will be summarized for all subjects. Summaries will include: the number of screen failures, 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

The following will be considered major protocol deviations as they could potentially affect the primary efficacy outcome:

- Did not meet all inclusion/exclusion criteria
- Used prohibited concomitant medications or therapies
- Missed treatment phase Visit 7 cycle 3 MBL analysis or Visit 8, cycle 6 MBL analysis
- Had treatment cycles collected out of window (> ± 2 days from the protocol specified start date)
- Had treatment cycles collected beyond validated product stability (>56 days)

7.3 Demographic and Baseline Characteristics

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

Demographic and baseline characteristics will be summarized for the Safety and MITT populations. If the Supportive MITT and/or the PP population size are noticeably different from the MITT, the demographic and baseline characteristics will be summarized for the Supportive MITT and/or 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 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

Exposure to study IUS will be summarized by treatment duration.

9. EFFICACY ANALYSES

The primary efficacy analysis will be based on the MITT population. Additional supportive efficacy analyses will be performed using the ITT (including and excluding subjects who are LTFU or withdrew consent without study IUS removal), Supportive

MITT, and PP populations, unless it is determined that the populations are essentially equivalent.

9.1 Menstrual Blood Loss

This study will utilize the AH method to assess MBL. During the Screening Phase all feminine hygiene products used during a menses with any evident bleeding will be analyzed. Baseline MBL will be the average of the Screening cycles evaluated. Two of three cycles must have ≥80 mL MBL to qualify for enrollment (Treatment Phase); if the first two cycles qualify a third cycle will not be evaluated. During the Treatment Phase, all feminine hygiene products use only during Cycle 3 (Days 57-84) and Cycle 6 (Days 141-168) will be collected for analysis and used to determine efficacy. All values of MBL reported by the lab for the above cycles for both validated and unvalidated feminine hygiene products will be included in the analysis, unless analyzed beyond the 56 days of validated stability.

MBL assessment measured from all collected feminine hygiene products will be included in the primary analysis and only study-specific validated feminine hygiene products in the supportive analyses.

The study-specific feminine hygiene products are:

- Tampax Regular Tampons with flushable applicator
- Tampax Super or Super Plus tampons with flushable applicator
- Kotex Regular Maxi Pads;
- Kotex Super Long Maxi Pads;
- Kotex Overnight Maxi Pads with Wings.
- Carefree Body Shape Pantiliners with Actifresh, Extra Long

A MBL assessment by AH may not be collected for Treatment Phase Cycle 3 and Cycle 6 in which a subject reported being amenorrheic (no spotting or bleeding) on the CRF for AH Menstrual Blood Loss Assessment; in this case the corresponding MBL value will be set to 0 mL. In the case that no feminine hygiene products were used by the participant due to spotting only the MBL value will be set to 0 mL.

Any feminine hygiene product collection would be considered “invalid” for the following:

- Analyzed beyond the 56 days of validated stability (from start of feminine hygiene collection).
- Any feminine hygiene product collection for a Treatment Phase cycle for which it was discovered during the post-collection interval study visit (i.e., Visit 7 for Cycle 3 and Visit 8 for Cycle 6) that the study IUS was not present
- Technical issue at the lab in analyzing the product leading to unreportable results

9.2 Primary Efficacy Variables

The primary outcome measure will be the proportion of subjects with successful treatment of heavy menstrual bleeding based on the decrease in MBL from baseline to end of treatment after initial LNG20 IUS insertion. For the MITT and PP analysis populations, end of treatment will be defined as the last post baseline MBL value (either Treatment Cycle 3 or Treatment Cycle 6) recorded for the subject.

For the ITT-based analysis population, subjects who lack both a Treatment Cycle 3 and Treatment Cycle 6 MBL result will have the baseline MBL serve as the end of treatment recorded outcome.

A subject with successful treatment will be defined as:

- the end of treatment MBL <80 mL, and
- a decrease to a value of no greater than 50% of the baseline MBL.

9.3 Key Secondary Efficacy Variables

All key secondary outcomes will be summarized by descriptive statistics using the MITT Population except that the bleeding and/or spotting analyses will be summarized using both Safety and MITT Populations. The subgroup analysis of absolute change in the median MBL from baseline to End-of-study will assess differences for age, race/ethnicity, and BMI subgroups, no formal statistical testing will be performed.

Menstrual Blood Loss:

- Absolute change in baseline MBL to mid-treatment MBL (Cycle 3)
- Percent change from baseline MBL to mid-treatment MBL (Cycle 3)
- Absolute change from baseline to end of treatment (Cycle 6), including subgroup analysis for age, race/ethnicity, and BMI

- Percent change from baseline MBL to end of treatment MBL (Cycle 6)

Vaginal Bleeding Flow:

- Vaginal bleeding flow (none, spotting, and light, normal, or heavy flow [bleeding]) will be summarized based on the daily diary by incidence and duration of bleeding at each Cycle. Vaginal bleeding is recorded on the daily diary during the Screening Phase and baseline will be considered the cycle with the worst flow severity during the screening cycles.
    - Based on World Health Organization (WHO) terminology, bleeding and spotting are defined as:
        - Bleeding: any bloody vaginal discharge for which protection, such as pads is used
        - Spotting: any bloody vaginal discharge for which protection is not used; if spotting and bleeding occur on the same day, it is recorded as a bleeding day
    - Incidence of bleeding by 28-day cycle 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) will be summarized

- Vaginal Bleeding Episodes
    - Based on the individual subject's daily dairy of bleeding
        - A bleeding day is when sanitary protection is used
        - A bleeding episode is defined as light, normal or heavy bleeding during a minimum of one day as defined by a subject's subjective assessment
        - A bleeding-free day is defined as a day with either no bleeding or only spotting
        - A single bleeding episode will consist of all bleeding days separated by no more than one bleeding-free day. Separate bleeding episodes will consist of bleeding days separated by more than one bleeding-free day. An episode will be considered stopped with two consecutive bleeding-free days.

- Bleeding will be summarized by the number and percentage of days with a particular pattern during each 28-Day interval after enrollment through Cycle 6 or IUS Discontinuation.
- Absolute changes and percentage changes from baseline to Cycle 3, from baseline to Cycle 6, and from Cycle 3 to Cycle 6 of the Treatment Phase will be calculated for the following bleeding pattern indices:
    - Total number of days of bleeding
    - Total number of days that include spotting or bleeding
    - Total number of days that include spotting only
    - Total number of bleeding episodes
    - The baseline numbers are the average of the Screening cycles evaluated

The subjective assessment of the impact of the LNG20 IUS on menstrual bleeding severity, dysmenorrhea, pelvic pain and daily activities will be assessed using a 10 cm Visual Analog Scale (VAS) questionnaire with appropriate questions. The VAS questionnaires will be completed and collected at baseline (Visit 5), and after 3 cycles (Visit 7) and 6 cycles (Visit 8):

- VAS scores for each question will be summarized for baseline, Cycle 3, and Cycle 6.
- VAS changes from baseline to mid-treatment (Cycle 3), from mid-treatment (Cycle 3) to end of treatment (Cycle 6) and from baseline to end of treatment (Cycle 6) will be summarized for each question.

10. METHODS OF EFFICACY ANALYSIS

10.1 Primary Efficacy Outcome

The primary efficacy analysis of the proportion of subjects with successful treatment of HMB from baseline to end of treatment (based on the last post baseline MBL value up to Treatment Cycle 6) will be presented with 95% confidence interval based on normal approximation of binomial distribution.

Subjects who are lost-to-follow-up (LTFU) or withdrew consent prior to Treatment Cycle 6 evaluation are considered a subset with truly missing information. In particular, within

the context of the Covid-19 pandemic, it could be reasonably argued that they may simply have been unable or unwilling to appear for an investigational site visit. Therefore, in order to evaluate the appropriateness of procedures for handling missing data, the following approaches to data analysis will be used (as described in SAP Sections 5.3.3 and 6):

1. MITT population with LOCF: results from this approach will be considered the principal analysis finding for this study.
2. ITT population with LOCF.
3. ITT population excluding subjects LTFU or withdrew consent without study IUS removal with LOCF.

Additional assessments using the supportive MITT and PP populations will be conducted as mentioned in SAP Section 6.

10.2 Secondary Efficacy Outcomes

All secondary efficacy outcomes will be summarized by descriptive statistics using the MITT Population except that the bleeding and/or spotting analyses will be summarized using both Safety and MITT Populations. Additional summaries will be provided for the median MBL change from baseline to End-of-study for subgroups such as age (18 to ≤35 and ≥ 36 yo), race/ethnicity, and BMI (<25, 25 to <30, or ≥30).

11. SAFETY ANALYSIS

All safety analyses will be based on the Safety population.

11.1 Adverse Events

Menstrual bleeding and cramping/pain are recorded in a daily subject diary and not on the Adverse Events CRF. 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

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 the safety contact 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”. All adverse events will be summarized with special attention to those events that may be related to an IUS, including:
    - Uterine perforation;
    - Low abdominal pain (not classified as dysmenorrhea or related to insertion/removal);
    - Pelvic infection (including uterine infection, PID and endometritis); and
    - Other urogenital infections
- 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.

11.2 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 for 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)

11.3 Menstrual Related Cramping/Pain

A subject will be defined as having menstrual cramping/pain (dysmenorrhea) TEAE if the subject diary question, "Check box if cramping today is more severe than your normal worst cramping" is marked.

Subject incidence of cramping/pain or dysmenorrhea TEAEs will be described within the overall adverse event incidence summary.

Dysmenorrhea (none, mild, moderate, or severe) will be summarized by the number and percentage of days with a particular pattern during each 28-Day interval after enrollment through end of Cycle 6 or IUS Discontinuation. In addition, dysmenorrhea changes from baseline (as established by the worst cramping during the screening cycles) will be summarized using shift tables.

For each 28-day cycle the incidence of on-treatment cramping/pain (none, mild, moderate, severe) 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 intervals post-insertion (none vs. ≥1 day; 1-3, 4-7, >7, and >20 days)
- Incidence of cramping/pain by highest severity by cycle 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 during each 28-day cycle. 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.

11.4 Menstrual Related Bleeding

A subject will be defined as having a menstrual Bleeding TEAE if the subject diary question, “Check box if bleeding today is more severe than your normal heaviest flow” is marked.

Subject incidence of bleeding TEAEs will be described within the overall adverse event incidence summary.

11.5 Insertion

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

Summaries will also be presented 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 meet the protocol defined IUS insertion failure, which is when, after advancing through the external 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

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.

11.6 Continuation, Expulsion, and Removal Rates

Cumulative rates of IUS continuation, expulsion, and safety-related removal at 1 month (Visit 6), 3 months (Visit 7) and 6 months (Visit 8) will be summarized and analyzed using Kaplan-Meier methods. 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 in the Safety Population will also be summarized.

11.7 Pelvic and Breast Examinations

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

11.8 Clinical Laboratory Evaluation

11.8.1 Hemoglobin/Hematocrit/Ferritin

The percent change in hemoglobin, hematocrit and serum ferritin will be summarized using descriptive statistics:

- from baseline to mid-treatment (Visit 7)
- from baseline to end of treatment (Visit 8)
- from mid-treatment (Visit 7) to end of treatment (Visit 8)

11.8.2 Chlamydia and Gonorrhea Evaluations

The frequency and percentage of Chlamydia and gonorrhea results will be summarized.

11.8.3 Urine Pregnancy Tests

Urine pregnancy tests will be listed by subject.

11.8.4 Other Baseline Laboratory Testing

Serum chemistry (basic metabolic panel), FSH, TSH, PRL, vWF, ALT, and AST results are collected during the Screening Phase and will be listed by subject.

11.9 Vital Signs

Blood pressure, pulse 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. Height will only be presented in listings.

12. REFERENCES

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3. Kaunitz MA, Bissonnette F, Monteiro I, Lukkari-Lax E, DeSanctis Y, Jensen JT, Levonorgestrel-Releasing Intrauterine System for Heavy Menstrual Bleeding Improves Hemoglobin and Ferritin Levels. Contraception 2012;86:452-457

APPENDIX A: STATISTICAL ANALYIS PLAN SUMMARY OF CHANGES

Any administrative changes to the protocol including spelling corrections, minor clarifications, renumbering, and reformatting are not summarized in the following table.

Section	Change to Statistical Analysis Plan	Rationale
Title Page, Signature Page	Date and version # changed	The date and version # changed due to this revision.
	Updated the address for Medicines360.	[redacted]
Abbreviations	Added BOCF for Baseline observation carried forward	
	Added ITT: Intent-to-Treat	For completeness
	Added LTFU: Lost-to-follow-up	For completeness
Definitions	Added light bleeding but no product use to definition of amenorrhea	A woman may subjectively consider her bleeding to be light and not us any sanitary products.
	Added ITT	To clarify analysis population
	Revised MITT	To clarify analysis population
	Revised Supportive MITT	To clarify analysis population
	Revised PP	To clarify analysis population
Section 3	Described allowed delays in collecting screening cycles due to the pandemic	COVID-19 mitigation

Section 5.3.3	Added more detailed explanation of how MBL will be calculated when no feminine hygiene products are collected due being amenorrheic for the 28-day collection cycle	To provide clarity
Sections 5.9, 9.3 and 10.2	Revised subgroup analysis by Wilcoxon testing to using descriptive statistics.	Subgroups were not assigned according to randomization so Wilcoxon testing is not applicable
Sections 5.9 and 10.2	Revised age subgroups	To provide clarity
Section 6	Added analysis populations of ITT and ITT excluding LTFU and WC without IUS removal	[redacted]
Section 9	Added ITT to efficacy analysis	
Sections 9.2 and 10.1	Revised end of treatment to be last post baseline MBL value up to Treatment Cycle 6	For clarity.
Section 10.1	Added LOCF parameters to the MITT and ITT analyses groups.	For clarity.