TITLE PAGE

Title:	A Phase 3, Multicenter, Open-Label Study of a Levonorgestrel 52 mg Intrauterine System for the Treatment of Heavy Menstrual Bleeding
Test Product:	LNG20 IUS (levonorgestrel-releasing intrauterine system)
IND	105,836
Indication	For the treatment of heavy menstrual bleeding
Protocol Number:	M360-L105
Investigators	Multicenter
Development Phase:	Phase 3
Study Design:	Open-Label
Sponsor:	Medicines360
Sponsor's Medical Officer:	[redacted]
Protocol Date:	05 February 2020
Version Number:	Version 4.0 Replaces version 3.0 dated 01 November 2018

SIGNATURE PAGE

Clinical Protocol M360-L105

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

Version 4.0
Dated: 05 February 2020

APPROVAL SIGNATURES

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PROTOCOL SYNOPSIS

Study Title	A Phase 3, Multicenter, Open-Label Study of a Levonorgestrel 52 mg Intrauterine System for the Treatment of Heavy Menstrual Bleeding
Short Title	LNG20 IUS Phase 3 study for heavy menstrual bleeding
Study Sponsor	Medicines360
Protocol Number	M360-L105
Study Phase	3
Study Objectives	Primary objective: Assess the efficacy of a levonorgestrel 52 mg intrauterine system (LNG20 IUS) as a treatment for heavy menstrual bleeding. Secondary objectives: Assess safety, tolerability, bleeding patterns, and continuation rates of LNG20 IUS in women using LNG20 IUS for heavy menstrual bleeding.
Planned Study Dates	Start of study/recruitment: October 2018 End of recruitment: December 2020 End of study treatment: July 2021 End of post-treatment follow-up: August 2021
Number of Investigative Sites	Approximately 30 sites in the U.S.
Number of Subjects Planned	Approximately 100 women between the ages of 18 and 50 years, inclusive, who request treatment for heavy menstrual bleeding, provide consent, and satisfy entry criteria will be enrolled for treatment.
Study Design	The study is a multicenter, open-label, evaluation of the efficacy and safety of LNG20 IUS for treatment of heavy menstrual bleeding. After consent is obtained, screening procedures will be performed and eligible subjects enrolled into the trial. The Screening Phase will include up to four visits (Visits 1 to 4) to evaluate menstrual blood loss (MBL) in

	up to three cycles to establish a diagnosis of heavy menstrual bleeding (MBL≥ 80 mL/cycle for two of three cycles) and confirm eligibility. Subjects will receive standardized feminine hygiene products and detailed instructions on how to record daily vaginal bleeding in a diary. Visit 1 will include consent and initial screening activities. Visits 2, 3 and 4 (if needed) will occur approximately monthly (ideally within 5 days of end of menses) to collect feminine hygiene products. The products will be evaluated using the alkaline hematin (AH) method to evaluate MBL. Subjects who have qualifying MBL in at least two of three screening cycles and who meet all other eligibility requirements may enter the six-month Treatment Phase (Visits 5 to 8). If the qualifying MBL occurs in the first two screening cycles, a third cycle and Visit 4 will not occur. The Enrollment Visit (Visit 5) is when IUS placement occurs. The study IUS will be inserted by a study Investigator using a standardized insertion procedure. Subjects will be evaluated during study treatment use for up to approximately 6 months. Study assessments will be performed at a clinic visit at Treatment Phase Month 1 (Visit 6), and at the end of Cycle 3 (Visit 7) and Cycle 6 (Visit 8/study exit). The IUS will be removed when requested or when clinically indicated; if the IUS is removed before Cycle 6, Visit 8/study exit procedures will be completed at the visit for removal. At the end of the 6 cycle Treatment Phase, unless medically contraindicated, study participants may opt to either keep the IUS or have it removed by a study investigator. All subjects who have the IUS removed during the study 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 (adverse event assessments and vital signs) will be conducted for all subjects at all protocol study visits.
Investigational Drugs:	A levonorgestrel 52 mg IUS (LNG20 IUS, marketed in the U.S. as Liletta®) with an initial levonorgestrel release rate of approximately 20 mcg/day will be evaluated. There will be no comparator.
Dosing Regimen:	A study Investigator will insert a LNG20 IUS into the uterus using standardized procedures in subjects who qualify after screening and desire to enroll. The IUS may be removed at any time if requested by the subject or judged necessary by the Investigator. Subjects who experience IUS expulsion (partial or complete) may have another study IUS inserted; only one replacement IUS is allowed per subject. Replacement can occur only if all of the following conditions are met: • Reinsertion occurs no more than 14 days after the expulsion; • Reinsertion occurs at least 7 days prior to treatment Cycle 3 or Cycle 6; • Reinsertion cannot occur during treatment Cycle 3 or Cycle 6; • Pregnancy can reasonably be excluded. An IUS removed during the study will not be replaced with a new LNG20 IUS except when the IUS is removed because of incorrect IUS placement at the enrollment visit (first attempt only) or within two weeks of an expulsion (complete or partial) during the Treatment Phase.
Primary Outcome Measure:	The proportion of subjects with successful treatment, defined as: • End of Treatment MBL < 80 mL, and • End of Treatment MBL 50% or less than baseline Baseline MBL is the MBL averaged over each of the cycles measured during the Screening Phase. End of Treatment MBL is the MBL during

	the sixth 28-day cycle after initial LNG20 IUS insertion. This outcome will be established in the Modified-Intent-To-Treat (MITT) population.
Key Secondary Outcome Measures:	Key secondary outcome measures will be: • Absolute change from baseline MBL to mid-treatment MBL (Cycle 3) • Percent change from baseline MBL to mid-treatment MBL (Cycle 3) • Absolute change from baseline MBL to end of treatment MBL (Cycle 6) • Percent change from baseline MBL to end of treatment MBL (Cycle 6) • 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) in the number of days of bleeding, spotting, bleeding and spotting, and number of bleeding episodes per cycle
Other Secondary Outcome Measures:	Other secondary outcomes that will be assessed for all subjects will include: • Percent change in hemoglobin, hematocrit and serum ferritin from baseline to mid-treatment (Visit 7), from baseline to end of treatment (Visit 8) and from mid-treatment (Visit 7) to end of treatment (Visit 8) • Continuation rate during Treatment Phase • Subjective assessment of menstrual bleeding changes • Adverse events
Duration of Subject Participation:	Up to approximately 12 months (up to 5 months screening, 6 months treatment, 1 month follow-up)
Duration of Study Center Participation:	Approximately 3.5 years (assuming 4 months for study start-up activities, an enrollment period of 24 months, up to 12 months subject participation followed by 4 months for study site close-out)

Eligibility Criteria:	Subjects must fulfill all of the following criteria to be eligible for study enrollment (Treatment Phase): **<u>Inclusion Criteria</u>** 1. Signed informed consent 2. Reports subjectively heavy menses for most menses when not using hormonal contraception or a copper IUD 3. Healthy females 18-50 years old, inclusive, at the time of enrollment 4. Able to read and write, as determined by study personnel 5. FSH value ≤30 mIU/mL at screening 6. Typical menstrual cycle length of 21-35 days with variation from cycle to cycle of typically 5 days or less 7. Has menstrual blood loss in 2 of the 3 cycles during the Screening Phase with ≥ 80 mL per cycle as measured by the AH method 8. Uterine sound depth of ≥5.5 cm 9. Willing to comply with study visit schedule and assessments, including sanitary product collection and diary completion requirements 10. Documented (i.e., printed report) Pap testing, regardless of subject's age, and any indicated evaluation/treatment that demonstrates no need for further evaluation during the course of study participation (i.e., within 10 months after consent) 11. Planning to reside within a reasonable driving distance of a research site (approximately 150 miles) for duration of study participation 12. Willing to use a medication other than a NSAID as first-line treatment for any pain condition during the duration of study participation 13. Willing to abstain from heterosexual intercourse or use acceptable contraception during the screening phase; acceptable

	contraception includes male or female permanent contraception, withdrawal (if has been using as current method prior to screening) or a barrier method 14. If previously pregnant, at least one subjectively heavy menses prior to screening **Exclusion Criteria** 1. Currently pregnant 2. Planning to attempt to become pregnant during the screening and treatment phases of study participation (i.e., up to approximately 11 months after consent) 3. Currently lactating or not having a subjectively heavy menses since discontinuation of lactation prior to screening 4. Clinical diagnosis of perimenopause (in the opinion of the investigator) based on one or more of the following: changes in menstrual regularity (e.g., shorter, longer, absent, irregular), hot flashes, sleeping disorder, or changes in mood (e.g., depression, nervous tension, and irritability) within 3 months prior to or during the screening period 5. Screening blood laboratory value outside of the normal range that, in the opinion of the investigator, requires treatment or further work-up (i.e., are considered clinically significant) 6. Has poor venous access or significant history of inability to have blood samples drawn 7. Body habitus or history of lower genital tract abnormalities or prior surgeries which may prohibit proper visualization of the cervix or not allow the uterus to be appropriately instrumented 8. History of bicornuate uterus or any other abnormality of the uterus resulting in distortion of the uterine cavity or cervical canal incompatible with insertion

	9. Prior (documented within 6 months) or baseline study ultrasound examination demonstrating: a. A congenital or acquired uterine anomaly that distorts the uterine cavity or cervical canal incompatible with insertion; b. Endometrial polyps (unless previously removed), c. Fibroids meeting any of the following criteria: i. Distort the uterine cavity or cervical canal incompatible with insertion; ii. Submucosal location; iii. Exceeding 2 cm in the greatest dimension for any individual fibroid; iv. More than three fibroids of at least 1.5 cm in greatest diameter d. Clear evidence of adenomyosis consisting of any of the following: i. Subendometrial cysts ii. Diffuse adenomyosis based on a heterogeneous myometrial echotexture consisting of: 1. Hyperechoic findings (islands of endometrial glands); 2. Hypoechoic findings (associated muscle hypertrophy); 3. "Venetian blind" appearance due to subendometrial echogenic linear striations and acoustic shadowing where endometrial tissues cause a hyperplastic reaction 10. Recently diagnosed or clinically evident cervicitis or upper genital tract infection at the time of IUS insertion (unless successfully

	treated and considered clinically cured for at least 7 days prior to enrollment) 11. History of pelvic actinomycosis infection (i.e., received antibiotic treatment; criterion does not include solely a history of Pap test with actinomyces) 12. Postpartum or post-abortion endometritis unless symptoms resolved at least 4 weeks prior to screening 13. Chronic endometritis on endometrial biopsy at screening (an endometrial biopsy performed within 6 months of Visit 1 could be used if a report is available with a tissue diagnosis) 14. Has any of the following premalignant or malignant diseases: a. Malignant melanoma b. Acute malignancies affecting blood or leukemias c. Gestational trophoblastic disease (unless at least one year with undetectable beta-hCG) d. Known or suspected cervical, ovarian, vaginal or vulvar cancer e. Uterine cancer or evidence of uterine malignancy, endometrial intraepithelial neoplasia (EIN) or hyperplasia on an endometrial biopsy at screening (an endometrial biopsy performed within 6 months of Visit 1 could be used if a report is available with a tissue diagnosis) f. History of breast cancer, or suspicion of breast cancer until proven otherwise 15. Has any of the following medical conditions: a. Bleeding diathesis (inherited or acquired) b. History of von Willebrand's disease or other known coagulopathy

	c. Uncontrolled significant hypertension defined as a sitting systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 95 mm Hg at any screening or enrollment visit unless treated and controlled within two weeks of discovery d. Presence or history of venous thromboembolic diseases (deep vein thrombosis, pulmonary embolism), presence or history of arterial thromboembolic diseases (e.g., myocardial infarction, stroke) e. Uncontrolled thyroid disorder f. Sickle cell anemia g. Diabetes mellitus that is poorly controlled or with end-organ/vascular complications h. Hyperprolactinemia at screening i. Acute or severe liver disease or liver tumor j. Poorly controlled bipolar disorder, schizophrenia, psychosis, major depressive disorder or other major psychiatric disorder according the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-5) k. History of a positive HIV test or having a partner who is known to be HIV positive l. Current or history of alcohol, illicit drug or prescription drug abuse within 12 months prior to screening 16. Use of antifibrinolytics, platelet aggregation inhibitors, anticoagulants or other similar medications that can increase or decrease bleeding within 30 days prior to and during the screening (*EXCEPTION: NSAIDs can be used as second-line treatment for pain management*)

	17. Use of intrauterine or implantable contraception, progestin-only pills, combined hormonal contraceptives or oral progestin therapy within 30 days before screening 18. Depomedroxyprogesterone acetate (DMPA) injection within the past 9 months prior to screening (this exclusionary time period can be shortened to 6 months if the subject has also had two spontaneous menstrual cycles [requires minimum of 3 heavy menses] that meet criteria for normal menstrual cycle pattern) 19. Use of non-contraceptive estrogen, progesterone, progestin, testosterone, androgen or other gonadotropins (e.g. hCG) within 30 days before screening 20. Prior total or partial endometrial ablation or resection 21. History of a uterine aspiration or curettage procedure for any indication (other than an office biopsy) within 4 weeks of screening 22. Known or suspected allergy to levonorgestrel or hypersensitivity to any component of the product 23. Use of an experimental medication or receipt of an experimental treatment for any condition within 30 days of screening 24. Study staff or a member of the immediate family of a study staff 25. Any condition or circumstance that, in the opinion of the Investigator, would constitute contraindications to participation in the study or would compromise ability to comply with the study protocol, such as any concurrent medical condition that is not stable and well-controlled, that is likely to worsen, or that may require recurrent hospitalizations during study participation
Statistical Methods:	The following analysis populations will be created: • Safety (Safety): All subjects enrolled who underwent the IUS insertion procedure, regardless of outcome.

	• Modified-Intent-To-Treat (MITT): Those subjects with successful IUS placement followed by at least one MBL assessment. • Per Protocol (PP): A subset of the MITT population that excludes subjects with major protocol deviations (to be identified prior to data lock). Each treatment cycle will be considered as a 28-day interval with the day of IUS placement as day 1. The primary efficacy analysis of successful treatment rate will be analyzed with 95% confidence interval for subjects in the MITT population. A point estimate of 80% or higher successful treatment rate with a lower bound of 70% or higher will establish the efficacy of LNG20 IUS for the treatment of heavy menstrual bleeding in the study. All other secondary endpoint analyses will be descriptive. All treatment emergent adverse event data will be presented by MedDRA system organ class, preferred term and treatment group. Quantitative safety variables (e.g., vital signs) will be summarized at each visit and by changes from baseline.
Sample Size:	Approximately 100 women will be enrolled into the study treatment phase with the goal that 85 women will complete the study to achieve the lower bound 70% or higher of a two-sided 95% confidence interval for an anticipated successful treatment rate 80% or higher.

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ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
AH	Alkaline hematin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
C	Celsius
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CHC	Combined hormonal contraceptives
CI	Confidence interval
cm	Centimeter
COC	Combined oral contraceptive
CRF	Case Report Form
dL	Deciliter
DMPA	Depomedroxyprogesterone Acetate
EDC	Electronic data capture
eCRF	Electronic Case Report Form
EIN	Endometrial intraepithelial neoplasia
F	Fahrenheit
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin
Hg	Mercury
HIV	Human immunodeficiency virus
HMB	Heavy menstrual bleeding
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

IND	Investigational new drug
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
LNG	Levonorgestrel
LTFU	Lost to Follow-Up
MBL	Menstrual blood loss
mcg	Microgram
mg	Milligram
MedDRA	Medical Dictionary for Regulatory Activities
mIU	Milli-international Units
MITT	Modified-intent-to-treat
mL	Milliliter
mm	Millimeter
MMAS	Menorrhagia Multi-Attribute Scale
NDA	New drug application
NSAID	Nonsteroidal anti-inflammatory drug
PID	Pelvic inflammatory disease
PP	Per protocol
PRL	Prolactin
SAE	Serious adverse event
STI	Sexually transmitted infection
TSH	Thyroid stimulating hormone
US	United States
VAS	Visual Analog Scale
vWF	von Willebrand Factor
WHO	World Health Organization

1. INTRODUCTION

Normal menstrual blood loss (MBL) ranges between 20 and 60 mL/cycle. Heavy menstrual bleeding (HMB), formerly referred to as menorrhagia, is defined as excessive blood loss that occurs alone or in combination with other symptoms and has a negative impact on a woman's physical, social, emotional, and material quality of life (Qiu et al., 2014).

Approximately 30% of women are affected by HMB during their reproductive years, resulting in increased health costs (OHTAC, 2016). A variety of functional, structural, and non-structural conditions can cause HMB, including adenomyosis, leiomyomas, and coagulopathies as well as iatrogenic causes. In many women, the underlying cause of HMB is unknown and is referred to as functional HMB (Mawet et al., 2014). Heavy menstrual bleeding is commonly defined as MBL exceeding 80 mL of blood loss per cycle, although only about half of women who complain of HMB actually meet these criteria (Qiu et al., 2014; Bahamondes et al., 2015). Clinical guidelines recognize that because HMB has a major impact on a woman's quality of life, the diagnosis should be based on subjective measures rather than the objective measure of MBL (NCCWCH, 2007). However, the quantity of MBL is still important for predicting outcomes as iron depletion and anemia can occur when menstrual flow exceeds 60 and 120 mL, respectively (NCCWCH, 2007).

Although hysterectomy is the preferred option for definitive treatment for women with HMB, medical management is always indicated first; hysterectomy, like any major surgical procedure, has potential significant complications and incurs social and economic costs, including incompatibility with a woman's wish to remain fertile (Maybin and Critchley, 2015, 2016; OHTAC, 2016). Endometrial ablation emerged as a more conservative surgical treatment for HMB in the 1990's but still results in impaired fertility. Currently, reversible non-hormonal and hormonal medical treatments are available as first-line therapy for most women with HMB regardless of their desire for future fertility.

Non-hormonal treatments for HMB include antifibrinolytics and non-steroidal anti-inflammatory drugs (NSAIDs), which are off-label uses of these products in the U.S. Both antifibrinolytics and NSAIDs produce gastrointestinal side effects but only require dosing during periods of heavy menstrual flow. Tranexamic acid is an antifibrinolytic medication

that counteracts the degradation of fibrin clots that form to induce hemostasis during the menstrual phase. Nonsteroidal anti-inflammatory drugs inhibit cyclooxygenase and limit the production of inflammatory mediators that can lead to increased and prolonged tissue damage during menstruation (Maybin and Critchley, 2016).

Hormonal treatments for HMB include oral or injectable progestins, combined hormonal contraceptives (CHCs) and intrauterine systems (IUSs). CHCs decrease menstrual flow and reduced symptoms for women with HMB (Bahamondes et al., 2015). During the menstrual cycle, progesterone levels sharply decline in the absence of pregnancy and trigger an influx of inflammatory mediators into the endometrial environment, leading to shedding and menstruation. However, maintenance of progesterone levels, as with progestin-only therapies or contraceptives containing estrogen and progestin, limits endometrial inflammation and prevents menstruation, resulting in an effective HMB treatment (Maybin and Critchley, 2016). CHCs are available as oral pills taken daily, vaginal rings used monthly, or patches changed weekly.

In the early 1990s, the progestin-releasing IUS containing levonorgestrel (LNG) 52 mg emerged as an option for medical management of HMB. While combined oral contraceptives, NSAIDs, and antifibrinolytics can reduce MBL by 50% within a few cycles of treatment, a LNG 52 mg IUS can decrease menstrual loss by 71% within 6 months and up to 94% after 1 year. Additionally, the LNG IUS can lead to greater improvement in women's assessment of the effect of HMB on their daily routine and psychological and physical well-being compared to usual medical treatment (Gupta et al., 2013; Qiu et al., 2014; Maybin and Critchley, 2016; Kaunitz et al., 2010). An IUS has the additional advantage of a "fit and forget" method that increases patient compliance.

A substantial body of literature has demonstrated the efficacy of the LNG 52 mg IUS in the treatment of HMB, including idiopathic HMB, HMB associated with leiomyomas and adenomyosis, and abnormal uterine bleeding. In these studies, reductions in MBL, resolution of anemia, and improvements in health-related quality of life were noted. The LNG 52 mg IUS is considered a first-line treatment for HMB (Espey, 2013). Currently only one LNG IUS, Mirena®, is approved in the U.S. for HMB treatment in women who choose to use intrauterine contraception as their method of contraception (Mirena Package Insert). The

other approved LNG 52 mg IUS, LNG20 IUS (brand name Liletta®), is currently approved only for contraception in the U.S. although it is approved for HMB treatment in Europe and Africa (under the brand names Levosert®, Avibela®, Mireffik™, Benilexa™, Donasert™, Levonortis™, and Tresovelle™). If approved for HMB treatment in the U.S., LNG20 IUS would offer prescribers and patients another HMB treatment option. Other currently available lower-dose LNG IUS products are not approved for HMB treatment.

LNG20 IUS has been investigated in a Phase 3, multicenter, single-blind randomized trial in Europe to assess the non-inferiority as compared to Mirena in patients with HMB utilizing a pictorial blood loss chart to assess MBL. Enrollment of 280 subjects was completed in January 2009 and 50% were randomized to LNG20 IUS. LNG20 IUS substantially reduced MBL in these women and based on this trial was approved in 2012 for the treatment of HMB in multiple European countries. A review of all safety data in a *post hoc* analysis supports that LNG20 IUS was generally well tolerated in female subjects with HMB.

The LNG20 IUS consists of a T-shaped polyethylene frame (T-body) with a steroid reservoir around the vertical stem. The steroid reservoir is covered with a polydimethylsiloxane membrane which controls the release rate of levonorgestrel from the reservoir. The reservoir contains levonorgestrel 52 mg, providing an initial release rate of approximately 20 mcg/day (Creinin et al., 2016). A polypropylene monofilament blue thread is attached to the end of the vertical stem. Refer to the Investigator's Brochure for full details on the components of LNG20 IUS.

2. STUDY OBJECTIVES

This study is being performed to evaluate the Medicines360 levonorgestrel 52 mg IUS, LNG20 IUS. LNG20 IUS is expected to be an effective treatment of heavy menstrual bleeding.

2.1 Primary Objective

The primary objective of this study is to assess the impact of LNG20 IUS on menstrual blood loss (MBL) from baseline to 6 months (during the sixth 28-day cycle) after initial LNG20 IUS insertion in women with HMB. The primary outcome measure is the proportion of subjects

with successful treatment defined as:

- end of treatment MBL <80 mL, and
- end of treatment MBL 50% or less than baseline

2.2 Secondary Objectives

The secondary objectives of this study are to assess:

- The absolute change from baseline MBL to mid-treatment MBL (Cycle 3)
- The percent change from baseline MBL to mid-treatment MBL (Cycle 3)
- The absolute change from baseline MBL to end of treatment MBL (Cycle 6)
- The percent change from baseline MBL to end of treatment MBL (Cycle 6)
- Changes from baseline to mid-treatment Cycle 3, from baseline to end of treatment Cycle 6, and from mid-treatment Cycle 3 to end of treatment Cycle 6 in the number of days of bleeding, spotting, bleeding and spotting and number of bleeding episodes.
- Percent change in hemoglobin, hematocrit and serum ferritin from baseline to mid-treatment (Visit 7), from baseline to end of treatment (Visit 8), and from mid-treatment (Visit 7) to end of treatment (Visit 8)
- Continuation rate during Treatment Phase
- Subjective assessment of menstrual bleeding changes
- Adverse events

3. INVESTIGATIONAL 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.

Approximately 100 eligible women, 18-50 years of age, will be enrolled to receive LNG20 IUS. This study will not restrict enrollment based on parity, weight or 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 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 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 MBL of ≥80 mL/cycle in at least 2 of 3 cycles as assessed by the alkaline hematin (AH) method.

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 2-3 screening phase cycles.

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, then 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.

All screening cycles, including a repeated screening cycle, must be consecutive.

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 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. 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.

Participation will end at Visit 8 except for the following circumstances:

- The IUS was removed at Visit 8: these subjects will be contacted 7 to 10 days after the visit to assess bleeding and cramping after removal and any IUS-related or IUS procedure-related adverse events.
- Subjects with ongoing IUS-related adverse events after completion of the Treatment Phase 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.

3.1 Outcome Measures

3.1.1 Primary Outcome Measure

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 6 months (during the sixth 28-day cycle) after initial LNG20 IUS insertion. This outcome will be established in the Modified-Intent-To-Treat (MITT) population measuring the change in absolute value from baseline MBL to the end of treatment MBL. Baseline MBL is the MBL averaged over all of the cycles measured during the Screening Phase. A subject with successful treatment will be defined as:

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

3.1.2 Key Secondary Outcome Measures

Key secondary outcome measures will be:

- Absolute change from baseline MBL to mid-treatment MBL (Cycle 3)
- Percent change from baseline MBL to mid-treatment MBL (Cycle 3)
- Absolute change from baseline MBL to end of treatment MBL (Cycle 6)
- Percent change from baseline MBL to end of treatment MBL (Cycle 6)
- 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) in the number of days of bleeding, spotting, bleeding and spotting and number of bleeding episodes

3.1.3 Other Secondary Outcome Measures

Other secondary outcomes that will be assessed for all subjects will include:

- Percent change in hemoglobin, hematocrit and serum ferritin from baseline to mid-treatment (Visit 7), from baseline to end of treatment (Visit 8) and from mid-treatment (Visit 7) to end of treatment (Visit 8)
- Continuation rate during Treatment Phase
- Subjective assessment of menstrual bleeding changes
- Adverse events

4. STUDY POPULATION SELECTION

4.1 Subject Selection

Approximately 100 subjects who qualify after screening will be enrolled in this study. Study entry (enrollment) is defined as the initiation of a study IUS insertion procedure. Subjects must fulfill all of the inclusion criteria and not meet any of the exclusion criteria to be eligible for enrollment.

4.2 Inclusion Criteria

1. Signed informed consent
2. Reports subjectively heavy menses for most menses when not using hormonal contraception or a copper IUD
3. Healthy females 18-50 years old, inclusive, at the time of enrollment
4. Able to read and write, as determined by study personnel
5. FSH value ≤30 mIU/mL at screening
6. Typical menstrual cycle length of 21-35 days with variation from cycle to cycle of typically 5 days or less

7. Has withdrawal bleeding in 2 of the 3 cycles during the Screening Phase with ≥ 80 mL per cycle as measured by the AH method
8. Uterine sound depth of ≥5.5 cm
9. Willing to comply with study visit schedule and assessments, including sanitary product collection and diary completion requirements
10. Documented (i.e., printed report) Pap testing, regardless of subject's age, and any indicated evaluation/treatment that demonstrates no need for further evaluation during the course of study participation (i.e., within 10 months after consent)
11. Planning to reside within a reasonable driving distance of a research site (approximately 150 miles) for duration of study participation
12. Willing to use a medication other than a NSAID as first-line treatment for any pain condition during the duration of study participation
13. Willing to abstain from heterosexual intercourse or use acceptable contraception during the screening phase; acceptable contraception includes male or female permanent contraception, withdrawal (if has been using as current method prior to screening) or a barrier method
14. If previously pregnant, at least one subjectively heavy menses prior to screening

4.3 Exclusion Criteria

1. Currently pregnant
2. Planning to attempt to become pregnant during the screening and treatment phases (i.e., up to approximately 11 months after consent)
3. Currently lactating or not having a subjectively heavy menses since discontinuation of lactation prior to screening
4. Clinical diagnosis of perimenopause (in the opinion of the investigator) based on one or more of the following: changes in menstrual regularity (e.g., shorter, longer, absent, irregular), hot flashes, sleeping disorder, or changes in mood (e.g., depression, nervous tension, and irritability) within 3 months prior to or during the screening period

5. Screening blood laboratory value outside of the normal range that, in the opinion of the investigator, requires treatment or further work-up (i.e., are considered clinically significant)
6. Has poor venous access or significant history of inability to have blood samples drawn
7. Body habitus or history of lower genital tract abnormalities or prior surgeries which may prohibit proper visualization of the cervix or not allow the uterus to be appropriately instrumented
8. History of bicornuate uterus or any other abnormality of the uterus resulting in distortion of the uterine cavity or cervical canal incompatible with insertion
9. Prior (documented within 6 months) or baseline study ultrasound examination demonstrating:
    a. A congenital or acquired uterine anomaly that distorts the uterine cavity or cervical canal incompatible with insertion;
    b. Endometrial polyps (unless previously removed),
    c. Fibroids meeting any of the following criteria:
        i. Distort the uterine cavity or cervical canal incompatible with insertion;
        ii. Submucosal location;
        iii. Exceeding 2 cm in the greatest dimension for any individual fibroid;
        iv. More than three fibroids of at least 1.5 cm in greatest diameter
    d. Clear evidence of adenomyosis consisting of any of the following:
        i. Subendometrial cysts
        ii. Diffuse adenomyosis based on a heterogeneous myometrial echotexture consisting of:
            1. Hyperechoic findings (islands of endometrial glands);
            2. Hypoechoic findings (associated muscle hypertrophy);
            3. "Venetian blind" appearance due to subendometrial echogenic linear striations and acoustic shadowing where endometrial tissues cause a hyperplastic reaction

10. Recently diagnosed or clinically evident cervicitis or upper genital tract infection at the time of IUS insertion (unless successfully treated and considered clinically cured for at least 7 days prior to enrollment)
11. History of pelvic actinomycosis infection (i.e., received antibiotic treatment; criterion does not include solely a history of Pap test with actinomyces)
12. Postpartum or post-abortion endometritis unless symptoms resolved at least 4 weeks prior to screening
13. Chronic endometritis on endometrial biopsy at screening (an endometrial biopsy performed within 6 months of Visit 1 could be used if a report is available with a tissue diagnosis)
14. Has any of the following premalignant or malignant diseases:
    a. Malignant melanoma
    b. Acute malignancies affecting blood or leukemias
    c. Gestational trophoblastic disease (unless at least one year with undetectable beta-hCG)
    d. Known or suspected cervical, ovarian, vaginal or vulvar cancer
    e. Uterine cancer or evidence of uterine malignancy, endometrial intraepithelial neoplasia (EIN) or hyperplasia on an endometrial biopsy at screening (an endometrial biopsy performed within 6 months of Visit 1 could be used if a report is available with a tissue diagnosis)
    f. History of breast cancer, or suspicion of breast cancer until proven otherwise
15. Has any of the following medical conditions:
    a. Bleeding diathesis (inherited or acquired)
    b. History of von Willebrand's disease or other known coagulopathy
    c. Uncontrolled significant hypertension defined as a sitting systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 95 mm Hg at any screening or enrollment visit unless treated and controlled within two weeks of discovery

d. Presence or history of venous thromboembolic diseases (deep vein thrombosis, pulmonary embolism), presence or history of arterial thromboembolic diseases (e.g., myocardial infarction, stroke)
e. Uncontrolled thyroid disorder
f. Sickle cell anemia
g. Diabetes mellitus that is poorly controlled or with end-organ/vascular complications
h. Hyperprolactinemia at screening
i. Acute or severe liver disease or liver tumor
j. Poorly controlled bipolar disorder, schizophrenia, psychosis, major depressive disorder or other major psychiatric disorder according the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-5)
k. History of a positive HIV test or having a partner who is known to be HIV positive
l. Current or history of alcohol, illicit drug or prescription drug abuse within 12 months prior to screening

16. Use of antifibrinolytics, platelet aggregation inhibitors, anticoagulants or other similar medications that can increase or decrease bleeding within 30 days prior to or during screening (*EXCEPTION: NSAIDs can be used as second-line treatment for pain management*)
17. Use of intrauterine or implantable contraception, progestin-only pills, combined hormonal contraceptives or oral progestin therapy within 30 days before screening
18. Depomedroxyprogesterone acetate (DMPA) injection within the past 9 months prior to screening (this exclusionary time period can be shortened to 6 months if the subject has also had two spontaneous menstrual cycles [requires minimum of 3 heavy menses] that meet criteria for normal menstrual cycle pattern)
19. Use of non-contraceptive estrogen, progesterone, progestin, testosterone, androgen or other gonadotropins (e.g. hCG) within 30 days before screening
20. Prior total or partial endometrial ablation or resection

21. History of a uterine aspiration or curettage procedure for any indication (other than an office biopsy) within 4 weeks of screening
22. Known or suspected allergy to levonorgestrel or hypersensitivity to any component of the product
23. Use of an experimental medication or receipt of an experimental treatment for any condition within 30 days of screening
24. Study staff or a member of the immediate family of a study staff
25. Any condition or circumstance that, in the opinion of the Investigator, would constitute contraindications to participation in the study or would compromise ability to comply with the study protocol, such as any concurrent medical condition that is not stable and well-controlled, that is likely to worsen, or that may require recurrent hospitalizations during study participation

5. STUDY TREATMENT

5.1 LNG20 IUS (Dosage and Formulation)

This T-shaped polyethylene device contains levonorgestrel 52 mg. For further details, see the LNG20 IUS Investigator's Brochure.

5.2 IUS Supply and Administration

Each IUS is packaged as a single use sterile system. An inserter for placement of the IUS into the uterine cavity which does not remain in permanent contact with the subject is included in the sterile package with the IUS. The IUS with the inserter should be stored in its sterile sealed package until insertion.

See the Investigator's Brochure for LNG20 IUS product description, and insertion and removal instructions.

5.3 IUS Storage and Accountability

LNG20 IUS should be stored at 25°C (77°F); with excursions permitted between 15-30°C (59-86°F) [See USP Controlled Room Temperature] prior to use. Temperature excursions outside

of the permitted range must be reported to the Sponsor or designee. Study drug accountability, reconciliation and record maintenance are responsibilities that must be performed in accordance with all applicable regulatory requirements. All unused IUSs will be stored for inventory and collection. Storage and shipping procedures to return unused IUSs are detailed in the Study Reference Manual.

All expelled (when available) and removed IUSs will be stored. All retained used IUSs will be appropriately disposed of only after accountability verification by a study monitor.

5.4 IUS Replacement

Subjects experiencing an expulsion (complete or partial) may have another study IUS inserted; only one replacement IUS is allowed per subject. Two insertion attempts are allowed as long as replacement criteria are met for both attempts. Replacement can occur only if all of the following conditions are met:

- Reinsertion occurs no more than 14 days after the expulsion;
- Reinsertion occurs at least 7 days prior to treatment Cycle 3 or Cycle 6;
- Reinsertion cannot occur during treatment Cycle 3 or Cycle 6.
- Pregnancy can reasonably be excluded

5.5 Concomitant and Excluded Therapy

Concomitant medications are any prescription medications or over-the-counter preparations used by the subject beginning 30 days prior to screening through IUS discontinuation (Visit 8/Early Discontinuation) and for those subjects with continuing evaluation of an ongoing IUS-related or IUS procedure-related adverse event through resolution or stabilization. All concomitant medications, including excluded therapies, must be documented in the Concomitant Medication CRF. Subjects who use excluded therapies may require discontinuation from the study. The Medical Monitor should be contacted to discuss possible discontinuation of these subjects.

The following concomitant therapies are excluded while on study treatment:

- Hormonal contraceptives
    - *EXCEPTION: emergency contraception in any situation when the subject feels the IUS expelled, she subsequently had intercourse and was not using any other permitted method of contraception (e.g., barrier or sterilization)*

    - Subjects will not be discontinued from the study because of emergency contraceptive use if the IUS is eventually identified to be in the correct location in the uterine cavity
- Use of antifibrinolytics, platelet aggregation inhibitors, anticoagulants or other similar medications that can increase or decrease bleeding
    - *EXCEPTION: NSAIDs can be used as second-line treatment for pain management*. Acetaminophen should be the first line treatment for pain management but if not effective then NSAID use is allowed
- Iron or folate supplement use are allowed if currently in use at screening entry but initiation of any new iron or folate supplementation during study participation is allowed only for the treatment of clinically significant iron-deficiency anemia
- Any non-contraceptive estrogen, progesterone, testosterone, or gonadotropin (e.g. hCG)
- Misoprostol on the day before or day of IUS insertion or removal
- Any investigational treatment or medication other than the LNG20 IUS (experimental diagnostic testing is allowed but may not substitute for any study required evaluations)

5.6 Blinding

This is an unblinded, open-label study.

6. STUDY PROCEDURES

A flowchart of study screening assessments is in Appendix A and of enrollment and follow-up assessments in Appendix B.

6.1 Alkaline Hematin Menstrual Blood Loss Assessment

This study will utilize the AH method to assess MBL. Participants will be provided with branded study-specific feminine hygiene products to be used exclusively during study participation. During the Screening Phase all feminine hygiene products used during a menses with any evident bleeding will be collected for analysis, stored at room temperature and provided to the site. During the Treatment Phase, all feminine hygiene products used during only Cycles 3 and 6 will be collected for analysis. A daily bleeding diary will be completed indicating the highest level of bleeding experienced for each day. A venous blood sample will be obtained after each menses or cycle evaluated. The collected venous blood samples and feminine hygiene products will be shipped to KCAS, LCC laboratory for AH analysis after each Screening Phase Visits 2-4, as applicable, and Treatment Phase Visits 7 and 8. Used feminine hygiene products that are brought by the subject to the site that do not require analysis will be appropriately disposed of.

6.2 Feminine Hygiene Products

Each participant will be provided a sufficient supply of study-specific feminine hygiene products:

- 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

No other feminine hygiene products or brands can be used during the study.

6.3 Clinical Laboratory Tests

The site's local laboratory will be used for hematology, ferritin, vWF, TSH, FSH, prolactin, chemistry (basic metabolic panel), AST, ALT, Chlamydia, and gonorrhea testing (documented test results obtained within 30 days prior to Visit 1 are acceptable if applicable

laboratory normal ranges are available). Blood testing does not require fasting. Documented Pap test results indicating that no further testing or follow-up during the duration of study participation is indicated may be used for screening. Additionally, endometrial biopsies will be performed by the site (unless a documented biopsy result obtained within 6 months prior to screening is available). High sensitivity urine pregnancy testing may be performed in the clinic.

6.4 Screening Transvaginal Ultrasonography

A transvaginal ultrasound during initial screening (unless documented by a formal report within 6 months prior to screening) should document any uterine fibroid size and location and determine the presence of any uterine abnormality that may be exclusionary to eligibility.

6.5 Subjective Assessment of Menstrual Bleeding

The subject will complete subjective assessment of menstrual bleeding, pain and the impact of bleeding and pain on daily activities using VAS questionnaires at baseline (Visit 5), and after 3 cycles (Visit 7) and 6 cycles (Visit 8) of treatment.

6.6 IUS Insertion Definitions

Up to two insertion attempts are permitted.

- An **insertion attempt** starts with placement of the IUS inserter through the external cervical os. IUS insertion ends with completion of cutting the IUS threads following successful intrauterine IUS placement or IUS insertion failure.
    - **IUS insertion failure** is considered to occur when after the IUS inserter passes through the external os of the cervix and completion of IUS insertion is not achieved.
    - **Successful IUS insertion** is considered as retention of the IUS in the uterus through cutting of the strings, unless removed for incorrect placement as determined by ultrasound or other means within the duration of the same clinic visit; the day of successful IUS insertion is considered Study Day 1.

- Note that **IUS insertion** is the general process that starts with opening of the LNG20 IUS kit with the intent to perform an insertion. The insertion process may stop before IUS insertion is attempted (see definition above); in such circumstances, an IUS insertion attempt has not occurred. Examples of procedure discontinuation prior to an insertion attempt include:
    - notable defect upon inspection of the product
    - loss of product sterility
    - inability to sound the uterus
    - subject intolerance of the procedure prior to LNG20 IUS contact with the external cervical os

6.7 Screening

Screening is considered to start with the signing of the Informed Consent Form by the participant.

6.7.1 Screening Phase Procedures

All screening procedures must be performed before the Treatment Phase Enrollment (Visit 5) procedures. Screening will consist of up to 4 visits approximately 30 days apart; actual Screening visit timing is based on the occurrence of the individual subject's menses. Initial screening procedures must start within 30 days of obtaining written informed consent or the subject must be re-consented. Subject interview for past medical history, medications, demographics and venous access history, should be conducted prior to performing study required laboratory tests or ultrasonography so that those women not eligible based on non-invasive entry criteria are excluded without unnecessary invasive evaluations. If a subject is determined to be a screen failure any collected un-assayed used feminine hygiene products should be disposed. All screening cycles, including a repeated screening cycle, must be consecutive.

6.7.2 Screening Visit 1

Written informed consent will be obtained prior to conducting any study specific procedures.

The screening procedures should be completed in order (Parts A through E) and may occur on separate days. All activities for Visit 1 should be completed within the following time frames:

- 30 days of signing of consent for women not requiring cessation of exclusionary medications (see Section 4.3 Exclusionary Criteria #16, #17 & #19)
- 60 days of signing consent for women requiring cessation of exclusionary medications (see Section 4.3 Exclusionary Criteria #16, #17 & #19) and Parts C through F (Sections 6.7.2.3 through 6.7.2.6) should be delayed until at least 30 days after the medication is stopped.

6.7.2.1 Part A: Review of medical history

- Pre-screening questionnaire (Appendix C)
- Demographics
- Gynecologic history
- Menstrual history
- Medical history review including psychiatric history
- Concomitant medication review
- Verify if significant history of poor venous access

If the subject meets any exclusion criterion then the subject is a screen failure; do not proceed further.

6.7.2.2 Part B: Urine pregnancy testing

- High sensitivity urine pregnancy test (if test is positive then subject is a screen failure; do not proceed further)

6.7.2.3 Part C: Blood tests

- Collect blood sample for FSH, TSH, PRL, vWF, hematology panel, ferritin, ALT, AST, chemistry panel (if not performed and documented within 30 days prior to screening)
    - Blood testing does not require fasting
    - If unable to draw blood then the subject is a screen failure; do not proceed further

6.7.2.4 Part D: Initial exam

- Obtain blood pressure, pulse, height, weight
- Breast exam- suspicion of cancer would make subject a screen failure (may be rescreened if breast cancer is ruled out)
- Pelvic exam- assess if anatomy compatible with IUS insertion (except uterine sounding) and for any acute cervical infection

If the subject meets any exclusion criterion then the subject is a screen failure; do not proceed further. Discard blood test samples if fails Part C on the same day.

6.7.2.5 Part E: Pelvic assessments

- Pap test (if required)
- Chlamydia and gonorrhea testing for all subjects (should be vaginal swab ideally but urine test acceptable) if not performed and documented within 30 days prior to screening
- Transvaginal ultrasound (if not documented within 6 months)
    - If immediate interpretation is available review for any exclusion criteria (e.g., endometrial polyp, subendometrial cysts, adenomyosis, fibroids that distort the uterine cavity or cervical canal; submucosal location; exceeding 2 cm in the greatest dimension for any individual fibroid; more than three fibroids of at least 1.5 cm in greatest diameter, etc.)
- Perform endometrial biopsy (if not documented within 6 months)
    - Perform high sensitivity urine pregnancy test before biopsy if the biopsy is occurring at a visit at which a test has not already been performed; if test is positive, do not perform biopsy and subject is a screen failure
    - If unable to obtain biopsy then the subject is a screen failure

If the subject meets any exclusion criterion then the subject is a screen failure; do not proceed further. Discard blood, Pap or Chlamydia/gonorrhea test samples if subject fails Part D on the same day of the specimen collection.

6.7.2.6 Part F: Screening Visit 1 completion

The screening phase can proceed once all testing is obtained even if laboratory or testing results are not yet available. Review eligibility criteria and continue screening of women who meet eligibility criteria (except for pending test results).

- Dispense diary for daily bleeding and instruct subject on completion
- Dispense patient instructions, feminine hygiene products and feminine hygiene product collection kit
- Instruct subject on collection of all feminine hygiene products (pads, tampons and liners) used from onset to end of menses (excluding those products with no evident blood collection)
- Schedule Visit 2 based on anticipated end of next menses
    - Instruct subject to contact site with onset of next menses to confirm dates and reschedule Visit 2 if needed
- If the subject is having her menses during the initial screening Visit 1, the collection of feminine hygiene products should begin with the onset of her next menses

6.7.3 Screening Phase Cycle Assessment Visits:

6.7.3.1 Overview

- The diagnosis of HMB will be established in the 2-3 cycles of the screening phase. If she meets the diagnosis of HMB in the first two cycles, she will be enrolled into the Treatment Phase and the third cycle will not be performed (i.e., no Visit 4).
- Screening Visit 2, Visit 3 and Visit 4 are ideally expected to occur within 5 days after the end of menses for the site to collect the used feminine hygiene products and to obtain venous blood sampling for AH determination, but may occur up to 21 days after the end of her menses; otherwise she is a screen failure
- A Screening Cycle may be repeated. Only one screening cycle may be repeated. Any screening cycle collection that is assayed cannot be repeated. A screening cycle can be repeated under the following conditions:

- If 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, then that cycle collection may be discarded and the cycle collection repeated
- If subject indicates the use of non-study feminine hygiene products during a menses, and in the opinion of the Investigator these products contained a substantial volume of blood, 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)

- Subjects determined to be screen failures between study clinic visits should be contacted to inform them that their study participation is over

6.7.3.2 Between Screening Visits 1 and 2 (Review of any pending test results):

- Check daily for report of pending test results and review within 3 business days of receipt
- If any exclusion criterion is met:
  - Subject is to be discontinued as a screen failure: do not proceed further
  - Subject to be contacted to inform her that she is discontinued from the study (she does not need to return the dispensed feminine hygiene products)
- If a lab or test result is reported as unevaluable (e.g., insufficient quantity, lab error, etc.) subject should be asked to return as soon as possible for repeat testing (unscheduled visit). Alternatively, although less preferred, repeat testing may be performed at Visit 2.

6.7.3.3 Screening Visit 2 (Screening Cycle 1 MBL Collection)

- Review screening lab and test results if available and any repeat testing if required
  - If any results meet any exclusion criterion then the subject is a screen failure
- Blood pressure and pulse

- Interview for change in medical history status (e.g., new medical conditions)
- Obtain urine for high sensitivity pregnancy test (if test is positive then subject is a screen failure: do not proceed further)
- Chlamydia and gonorrhea testing for any subject following a change in sexual partner since the last study visit.
- Collect venous blood sample for AH (ideally within 5 days of end of menses)
    - If the blood draw for AH cannot be made within 21 days of the end of menses, the subject is a screen failure and any collected feminine hygiene products for Screening Cycle 1 should be disposed of
- Collect and review daily diary for completeness and verify menstrual flow severity
    - If needed, have subject correct any unclear or incomplete entries
    - The Investigator and study staff should discuss with the subject, while reviewing the diary, if this cycle represents a typical heavy cycle, if she used only study specific products, and if she collected all used products
    - The Investigator and staff should use this information to decide if the subject meets the criteria to submit the collection, repeat a cycle or be discontinued
        - If the Investigator determines the cycle should be repeated, no other cycle collections can be repeated
        - If the Investigator determines the specimen collection is likely less than 60 mL and chooses not to submit (e.g., the subject states this collection represents a typical very heavy cycle and she only returns 4 lightly stained pads), the subject should be discontinued
- Collect all used feminine hygiene products for shipping to KCAS lab
    - Interview subject for feminine hygiene collection compliance
    - Dispense feminine hygiene product collection kit
    - Ship collected feminine hygiene products and venous blood sample to KCAS Lab
- Dispense any needed additional feminine hygiene products and instruct subject on collection of all feminine hygiene products (pads, tampons and liners) used from onset to end of next menses (excluding those products with no blood collection)
- Scheduling of Visit 3:

- Schedule Visit 3 to occur ideally ≤5 days after the expected end of menses based on her menstrual history
- Instruct subject to contact site with onset of next menses to confirm dates and reschedule Visit 3 if needed

6.7.3.4 Between Screening Visits 2 and 3 (Review of Cycle 1 AH results)

- Check pending MBL reports daily starting at 7 business days after shipment and review within 3 business days of receipt
  - If MBL for Cycle 1 is ≥80 mL, Cycle 1 is a qualifying cycle and the subject may continue to Visit 3
  - If MBL for Cycle 1 is <80 mL but ≥60 mL, Cycle 1 is not a qualifying cycle but she may continue to Visit 3
  - If MBL for Cycle 1 is <60 mL, the subject is to be discontinued (screen failure) and contacted to inform her that she is discontinued from the study
  - If MBL results for Cycle 1 has not been reported before the scheduled visit the subject may continue to Visit 3

6.7.3.5 Visit 3 (Screening Cycle 2 MBL Collection)

- Blood pressure and pulse
- Interview for change in medical history status (e.g., new medical conditions)
- Obtain urine for high sensitivity pregnancy test (if test is positive then subject is a screen failure)
- Chlamydia and gonorrhea testing for any subject following a change in sexual partner since the last study visit.
- Collect venous blood sample for AH (ideally within 5 days of end of menses).
  - If the blood draw for AH cannot be made within 21 days of the end of menses, the subject is a screen failure and any collected feminine hygiene products for Screening Cycle 2 should be disposed of.
- Collect and review daily diary for completeness and verify menstrual flow severity
  - If needed, have subject correct any unclear or incomplete entries

- The Investigator and study staff should discuss with the subject, while reviewing the diary, if this cycle represents a typical heavy cycle, if she used only study specific products, and if she collected all used products
- The Investigator and staff should use this information to decide if the subject meets the criteria to submit the collection, repeat a cycle (if a cycle not previously repeated) or be discontinued
  - If the Investigator determines the cycle should be repeated, no other collections can be repeated
  - If the first cycle was repeated or between 60 to 79 mL, and the Investigator determines this specimen is likely less than 80 mL and chooses not to submit (e.g., the subject states this collection represents a typical very heavy cycle and she only returns 4 lightly stained pads), the subject should be discontinued

- Collect all used feminine hygiene products for shipping to KCAS lab
  - Interview subject for feminine hygiene collection compliance
  - Dispense feminine hygiene product collection kit
  - Ship collected feminine hygiene products and venous blood sample to KCAS Lab
- Dispense any needed additional feminine hygiene products and instruct subject on collection of all feminine hygiene products (pads, tampons and liners) used from onset to end of next menses (excluding those products with no blood collection)
- Scheduling of Visit 4:
  - Schedule Visit 4 to occur ideally ≤5 days after end expected end of menses based on her menstrual history
  - Instruct subject to contact site with onset of next menses to confirm dates and reschedule Visit 4 if needed

6.7.3.6 Between Screening Visits 3 and 4 (Review of Cycle 2 AH results)

- Check pending MBL reports daily starting at 7 business days after shipment and review within 3 business days of receipt
  - If MBL for Cycle 2 is ≥80 mL, determine next visit based on Cycle 1 MBL:

- MBL for Cycle 1 was <80 mL, the subject may continue to Visit 4
- MBL for Cycle 1 was ≥80 mL, the subject meets MBL eligibility and Visit 4 is not to be performed
    - Contact subject to inform her the next visit will be for study IUS insertion and that she does not have to collect feminine hygiene products this cycle/discard any used feminine hygiene products from this cycle
    - Schedule for IUS insertion as per Visit 5 instructions (see Section 6.8.1)

- If MBL for Cycle 2 is <80 mL, determine next visit based on Cycle 1 MBL:
    - MBL for Cycle 1 was ≥80 mL, the subject may continue to Visit 4
    - MBL Cycle 1 was <80 mL the subject is to be discontinued (screen failure) and contacted to inform her that she is discontinued from the study
- If MBL for Cycle 2 has not been reported before the scheduled visit the subject may continue to Visit 4

6.7.3.7 Visit 4 (Screening Cycle 3 MBL Collection) – if necessary

- Blood pressure and pulse
- Interview for change in medical history status (e.g., new medical conditions)
- Obtain urine for high sensitivity pregnancy test (if test is positive then subject is a screen failure)
- Chlamydia and gonorrhea testing for any subject following a change in sexual partner since the last study visit
- Collect venous blood sample for AH (ideally within 5 days of end of menses)
    - If the blood draw for AH cannot be made within 21 days of the end of menses, the subject is a screen failure and any collected feminine hygiene products for Screening Cycle 3 should be disposed
- Collect and review daily diary for completeness and verify menstrual flow severity
    - If needed, have subject correct any unclear or incomplete entries

- The Investigator and study staff should discuss with the subject, while reviewing the diary, if this cycle represents a typical heavy cycle, if she used only study specific products, and if she collected all used products
- The Investigator and staff should use this information to decide if the subject meets the criteria to submit the collection, repeat a cycle (if a cycle not previously repeated) or be discontinued
  - If the Investigator determines the cycle should be repeated, no other collections can be repeated
  - If the Investigator determines this specimen is likely less than 80 mL and chooses not to submit (e.g., the subject states this collection represents a typical very heavy cycle and she only returns 4 lightly stained pads), the subject should be discontinued

- Collect all used hygiene products for shipping to KCAS lab
  - Interview subject for feminine hygiene collection compliance
  - Dispense additional hygiene products as needed
- Scheduling of Visit 5:
  - Schedule for IUS insertion at a time after expect to receive AH results and as per Visit 5 instructions (see Section 6.8.1)
  - Instruct subject to contact site with onset of next menses if occurs before next scheduled appointment
  - If the subject is unable to comply with the scheduling requirements then she is a screen failure; do not proceed further

6.7.3.8 Between Screening Visit 4 and Enrollment Visit 5 (Review of Cycle 3 AH results)

- Check pending test results for return daily starting at 7 business days after shipment and review within 3 business days of receipt
  - If MBL is ≥80 mL, the subject the subject meets MBL eligibility and continues to Visit 5 as scheduled
  - If MBL is <80 mL the subject is to be discontinued (screen failure) and contacted to inform her that she is discontinued from the study

6.8 Treatment Phase Enrollment Visit (Visit 5)

The Treatment Phase Visit 5 should occur within 45 days of the screening visit (i.e., Visit 3 or Visit 4) that determined eligibility. An IUS insertion attempt enrolls the subject into the Treatment Phase. Second insertion attempts are allowed and can occur on the same day or different day, but a second attempt must be within 30 days of the first attempt. The day of successful IUS insertion is considered Study Day 1.

6.8.1 Enrollment visit (insertion) scheduling

- The LNG20 IUS can be inserted at any time the provider is reasonable certain the woman is not pregnant. Consider the possibility of ovulation and conception prior to initiation of the product
- If the LNG20 IUS is inserted after the first 7 days of the menstrual cycle and the subject is not using permanent contraception, she should use a barrier contraceptive method or abstain from heterosexual vaginal intercourse for 7 days after insertion to prevent pregnancy

6.8.2 Enrollment Procedures

- Prior to IUS insertion attempt:
    - Review medical history changes since the prior visit
    - Review medication history changes since the prior visit
    - Obtain blood pressure, pulse and weight
    - Obtain high sensitivity urine pregnancy test (if test is positive then subject is a screen failure)
    - Confirm eligibility criteria
    - Subject completion of Baseline VAS questionnaire (Appendix D)
    - Collect venous blood sample for hemoglobin, hematocrit, ferritin
    - Perform pelvic exam (repeat exam if second insertion attempt on separate day)
        - Perform Chlamydia and gonorrhea testing if the subject has a new sexual partner since the Screening Phase Visit 1

- IUS insertion can occur without test results
- Women with positive tests should be contacted and receive treatment as soon as possible without waiting for the next study clinic visit

  - If a pelvic exam demonstrates signs of acute cervical or uterine infection, provide appropriate antibiotic treatment and postpone the insertion attempt until subject is considered clinically cured for at least 7 days
  - Vaginal infections (e.g., trichomaniasis, symptomatic bacterial vaginosis or symptomatic vaginal candidiasis) can be treated at the time of IUS insertion

- Insert the study IUS using the techniques described in the Investigator's Brochure
  - Up to two attempts for insertion can be made (on the same day or 30 days of each other)
    - If a second attempt is performed on a different day, repeat all steps listed under "Prior to IUS insertion attempt" except blood testing and VAS questionnaire
    - Each attempt should use a new IUS
  - If the IUS is unable to be inserted after two attempts or the uterus sounds to <5.5 cm:
    - If there are no AEs related to the insertion attempt (s), the subject will be discontinued from the study and is not required to have any subsequent study-related follow-up
    - If there are AEs related to the insertion attempt (s) the subject should be followed at appropriate intervals by clinic visit or telephone contact until the adverse event resolves or has stabilized, after which the subject can be discontinued from the study
- Evaluate for adverse events related to IUS placement procedure
- Distribute study-specific feminine hygiene products and diaries as needed
- Instruct subjects on the following

- How to correctly check for the IUS string in the vagina (subjects will not be required to routinely check for IUS placement but if a subject believes the IUS is expelled or no longer in the correct place, she can check for the IUS string if she desires)
- Do not use a Diva Cup to collect bleeding because it could cause IUS expulsion; only use the provided feminine hygiene products
- Call for an urgent study visit if she:
  - Suspects she is pregnant
  - Has expelled the IUS (if subject has the expelled IUS, she should bring it to the study site at the next visit)
  - Has symptoms of a pelvic infection
  - Attempts to feel the strings and cannot feel them
  - Believes she feels the IUS in her cervix or vagina
- If an urgent study visit is required, she should refrain from having sex or use appropriate non-hormonal contraception until a study evaluation is completed

- Counsel regarding STI precautions
- Schedule Visit 6 for 4 to 6 weeks after successful study IUS insertion (Day 28 to Day 42)
- Register subject in the Enrollment eCRF

6.9 Treatment Phase Visits and Contacts

All follow-up will be based on 28-day Cycles. Post-insertion study evaluations will occur at Treatment Phase Visit 6 (Day 28 to Day 42) and Visit 7 (Day 85 to Day 105).

6.9.1 Visit 6

- Timing: Day 28 to 42
- Procedures:
  - Review of adverse events or changes in medical history since the prior visit
  - Review of concomitant medications
  - Inquire about change in sexual partner

- Collect and review daily diary for completeness
- Dispense additional diaries and feminine hygiene products as needed
- Physical examination and testing
  - High sensitivity urine pregnancy test (if positive, see Section 7.4)
  - Blood pressure, pulse and weight
  - Any clinically indicated physical examination
  - Clinically verify presence of IUS by palpation or direct visualization of strings (for missing strings management see Section 6.13 and Appendix G)
  - Chlamydia and gonorrhea testing for any subject following a change in sexual partner since the last study visit
    - Women with positive tests should be contacted and receive treatment as soon as possible without waiting for the next study clinic visit
- Instruct her to start collecting all used feminine hygiene products with evident blood between Day 57 and Day 84
  - Day 57 would include any products initiated prior to going to sleep the night before but removed on Day 57
  - Any products initiated the evening of Day 84 but removed the next morning would not be collected
- Schedule next appointment (Visit 7) ideally for Day 85 to Day 89, but up to Day 105 is allowed

6.9.2 Contact Day 50 to Day 56

- Remind subject to:
  - Start collecting all used feminine hygiene products with evident blood collection between Day 57 and Day 84
    - Day 57 would include any products initiated prior to going to sleep the night before but removed on Day 57
    - Any products initiated the evening of Day 84 but removed the next morning would not be collected

- Dispose of any used products from prior to Day 57 or after Day 84
- Confirm date and time for Visit 7 appointment

6.9.3 Visit 7 (Cycle 3)

- Timing:
  - Ideal: Day 85 to 89 (Cycle 3, days 1-5)
  - Allowable: up to day 105 (Cycle 3, days 1-21)
- Follow-up Procedures:
  - Review of adverse events or changes in medical history since the prior visit
  - Review of concomitant medications
  - Inquire about change in sexual partner
  - Collect and review daily diary for completeness
  - Subject completion of Treatment VAS questionnaire (Appendix E)
  - Dispense additional diaries and feminine hygiene products as needed
  - Physical examination and testing
    - High sensitivity urine pregnancy test (if positive, see Section 7.4)
    - Blood pressure, pulse and weight
    - Any clinically indicated physical examination
    - Clinically verify presence of IUS by palpation or direct visualization of strings (for missing strings management see Section 6.13 and Appendix G)
    - Chlamydia and gonorrhea testing for any subject following a change in sexual partner since the last study visit.
      - Women with positive tests should be contacted and receive treatment as soon as possible without waiting for the next study clinic visit
  - Collect all feminine hygiene products collected between Day 57 and Day 84
  - Interview subject for feminine hygiene collection compliance
  - Collect venous blood for:
    - Hemoglobin/hematocrit and ferritin
    - AH assay sample

- Instruct her to start collecting all used feminine hygiene products with evident blood between Day 141 and Day 168
  - Day 141 would include any products initiated prior to going to sleep the night before but removed on Day 141
  - Any products initiated the evening of Day 168 but removed the next morning would not be collected
- Schedule next appointment (Visit 8) ideally for Day 169 to Day 174, but up to Day 189 is allowed

6.9.4 Contact Day 133 to Day 140

- Remind subject to:
  - Start collecting all used feminine hygiene products with evident blood collection between Day 141 and Day 168
    - Day 141 would include any products initiated prior to going to sleep the night before but removed on Day 141
    - Any products initiated the evening of Day 168 but removed the next morning would not be collected
  - Dispose of any used products from prior to Day 141 or after Day 168
  - Confirm date and time for Visit 8 appointment

6.10 Study Treatment Phase Completion/Early Discontinuation (Visit 8)

- Timing:
  - Completion of 6 cycles of LNG20 IUS use
    - Ideal: Day 169 to Day 174 (within 5 days of completing 6 cycles)
    - Allowable: up to Day 189 allowed (up to 21 days after completing 6 cycles)
  - Early discontinuation
- Procedures:
  - Review of adverse events or changes in medical history since the prior visit
  - Review of concomitant medications
  - Inquire about change in sexual partner
  - Collect and review daily diary for completeness

- Subject completion of Treatment VAS questionnaire
- High sensitivity urine pregnancy test (if positive, see Section 7.4)
- Weight, pulse and blood pressure
- Any clinically indicated physical examination
- Clinically verify presence of IUS by palpation or direct visualization of strings (for missing strings management see Section 6.13 and Appendix G)
- Chlamydia and gonorrhea testing for any subject following a change in sexual partner since the last study visit.
    - Women with positive tests should be contacted and receive treatment as soon as possible
- Breast and pelvic exam (if not performed within the last 3 months)
- IUS removal
    - If participant has contraindication to continuing IUS use or desires removal then perform IUS removal procedure
    - If no indication for removal, discuss option of continuing IUS or removal; remove IUS for all women that desire to discontinue IUS
- Retain all removed or expelled IUSs as described in the Study Reference Manual
- Collection of feminine hygiene products:
    - If completed full protocol: collect all products collected between Day 141 and Day 168
    - If early discontinuation coinciding with Visit 7 (Cycle 3): collect all products collected between Day 57 and Day 84
    - If early discontinuation not coinciding with a complete Visit 7 or Visit 8 collection window: no product collection
- If collected feminine hygiene products:
    - Interview subject for feminine hygiene collection compliance
    - Collect venous blood for:
        - hemoglobin/hematocrit and ferritin (if not obtained within the prior 6 weeks)
        - AH assay sample

6.11 Safety Follow-Up

All subjects for whom the IUS was removed will be contacted 7 to 10 days after the study exit visit to assess for any post-IUS removal bleeding and cramping (if applicable), 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.

6.12 Unscheduled Visits

Subjects may require an evaluation at times other than the scheduled visits. An unscheduled visit should only be conducted when the subject reports problems that are related to the IUS, study safety issues or if repeat laboratory testing is required. In such circumstances, the unscheduled visit should be performed by a study clinician to review any change in medical history and perform any examination and testing as clinically indicated.

6.13 Diagnostic Ultrasound Examinations

Diagnostic ultrasound examinations may be required during the study for pregnancy (see Appendix F), missing IUS strings (see Appendix G), confirmation of IUS location or possible IUS related adverse events. Any time an ultrasound examination is performed for diagnostic purposes, the image must be documented in a photo or digital image to be included in the source documentation. If the exam is not documented in a formal report, a high resolution copy of the image documentation should be forwarded within 5 business days for a verifying review by the Sponsor as described in the Study Reference Manual. All ultrasound findings should be documented as follows:

- Printed image(s) with the subject's study number on the image
- Indication, impression and plan related to the images written in the source documentation

All ultrasound examination documentation should be maintained with the subject's study source documentation.

For details regarding the sponsor review of study-related ultrasound exams see the Study Reference Manual.

6.14 Pap Testing

Screening Pap testing must demonstrate that no further evaluation or treatment is required during the course of study participation (i.e., within approximately 10 months after screening). A prior printed cytology report may be used in place of performing Pap testing at the Screening Visit 1.

6.15 Management of Abnormal Testing During the Study

Clinically significant study-related results should be managed as follows:

- Gonorrhea or Chlamydia: treatment in accordance with current Centers for Disease Control and Prevention (CDC) guidelines. The IUS should not be removed because of a positive test or a diagnosis of cervicitis
- Hemoglobin/hematocrit and ferritin: a value consistent with clinically significant anemia should be evaluated and treated within the local standard of care

6.16 Management of Unevaluable Testing During the Study

An unevaluable test is any test for which the sample or specimen could not produce a result.

- Screening Phase Tests:
    - Visit 2 allows for repeat of unevaluable tests
    - If the samples or specimens from Visit 2 are also unevaluable then repeat at Visit 3 – the results must be available and reviewed for eligibility prior to enrollment
- Treatment Phase Tests (including Treatment Phase Discontinuation/Early Discontinuation)
    - Unevaluable hemoglobin/hematocrit or ferritin should be repeated as soon as possible at an Unscheduled Visit

7. RISK-BENEFIT AND SAFETY ASSESSMENTS

7.1 Risk-Benefit

7.1.1 Menstrual Changes

Women with heavy menstrual bleeding who use a LNG 52 mg IUS generally experience a change in bleeding patterns with a trend toward reduction of MBL (Lethaby et al., 2009). The reduction in MBL with LNG 52 mg IUS is greater than that achieved with combined oral

contraceptives (COC), tranexamic acid, or long-course (≥3weeks/cycle) oral progestins (Bitzer et al., 2015).

In a randomized study comparing LNG 52 mg IUS to MPA over 6 months, approximately 85% of the LNG IUS users had successful treatment compared to 22% of MPA users. Treatment success was defined as achieving MBL of <80 mL and at least a 50% reduction from baseline. Additionally, bleeding was rated as significantly improved according to investigator assessment (93.6% LNG IUS vs. 61.0% MPA) and self-assessment (93.6% LNG IUS vs. 67.1% MPA) (Kaunitz et al., 2010). In a randomized study in Europe comparing LNG20 IUS to Mirena, both products produced similar reductions in MBL after the 6 months of study treatment (79.0% vs. 79.2%, respectively) (Mawet et al., 2014).

A study comparing the LNG 52 mg IUS to a usual-treatment group (tranexamic acid, mefenamic acid, COC or oral progesterone) demonstrated that improvements as measured by the patient-reported Menorrhagia Multi-Attribute Scale (MMAS) were significantly higher at the end of 6 months of treatment with the LNG IUS group compared to the usual treatment group (32.7 points and 21.4 points, respectively). Additionally, improvements in all MMAS domains (practical difficulties, social life, family life, work and daily routine, psychological well-being, and physical health) were significantly better for the LNG IUS group. At the end of two-years 64% of the LNG IUS group continued to use the product compared to 38% of the usual-treatment group (Gupta et al., 2013).

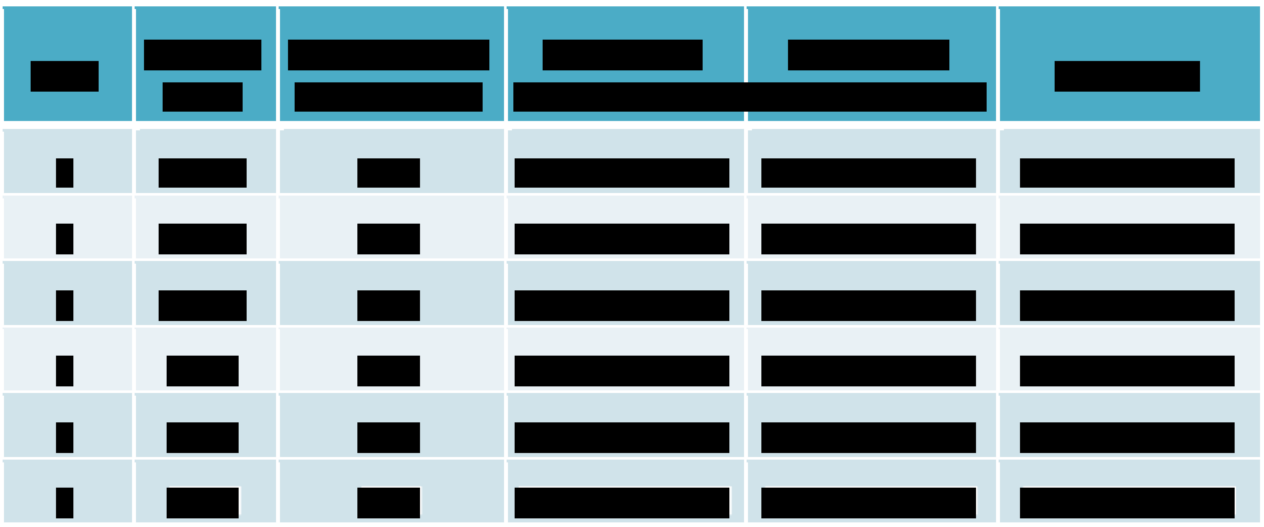
Hemoglobin and ferritin values increase with LNG 52 mg IUS use in women with HMB. In a randomized study assessing the efficacy of a LNG IUS and oral MPA (10 mg/day for 10 days) in women with confirmed HMB, hemoglobin and serum ferritin levels were assessed at baseline, and at Cycles 3 and 6 of treatment. Baseline median hemoglobin and ferritin levels were 12.4 g/dL and 19.0 mcg/L with the LNG IUS and 12.2 g/dL and 19.0 mcg/L with oral MPA, respectively. At Cycle 6, the corresponding medians were 13.4 g/dL and 34.0 mcg/L with the LNG IUS and 12.6 g/dL and 21.0 mcg/L with oral MPA (Kaunitz et al., 2010). The increases from baseline to Cycle 6 were greater in the LNG IUS group than in the oral MPA group for hemoglobin levels (7.5% vs. 1.9%; p<.001) and median serum ferritin levels (68.8% vs. 14.3%; p<.001).

Of note, amenorrhea rates in women who use the LNG 52 mg IUS for HMB are lower than the rates reported in women who use the LNG 52 mg IUS primarily for contraception. In contracepting women, approximately 20% of women are amenorrheic for a period of 90 days or more by the end of the first year of use (Andersson et al., 1994, Schreiber et al., 2018); this amenorrhea rate is reached within about 9 months of use (Schreiber et al., 2018). Pooled data from four randomized trials comparing the levonorgestrel 52 mg IUS to medroxyprogesterone acetate orally, tranexamic acid orally, mefenamic acid orally and endometrial resection in 163 women with HMB demonstrates the change in bleeding seen in this specific population (Jensen et al., 2013). Amenorrhea rates in this population were 2% at 6 months and 9% at one year. By one year, an additional 24% were reporting infrequent bleeding/spotting. Only 6% of women using the LNG 52 mg IUS for HMB in these trials discontinued for bleeding complaints.

Overall, participants are expected to primarily experience a reduction in flow with study product use.

7.1.2 Contraception

Subjects at risk for pregnancy should be using a contraceptive method during screening phase. However, during the Treatment Phase, subjects are not required to use a contraceptive other than the LNG20 IUS. Any method of contraception may not prevent pregnancy. LNG20 IUS is currently FDA-approved for contraception for up to 6 years of use. [redacted]



7.1.3 Pregnancy

If pregnancy occurs during study treatment, the subject will be instructed that the LNG20 IUS should be removed in accordance with standard medical care. The investigator will discuss with the subject all pregnancy options and will provide information regarding providers and health care facilities. Pregnancy management is outlined in Appendix F.

All pregnancies that occur while a subject is using the study IUS will be followed to completion. Pregnancy outcomes, including normal births, septic abortions, ectopic pregnancies, birth defects, and premature deliveries, whenever this information can be obtained for all women who get pregnant during the study.

7.1.3.1 Miscarriage

Women who become pregnant and miscarry while using an LNG IUS are rarely reported in the literature. The overall number of reports is too low to understand whether the risk is the same or different than the risk of spontaneous abortion in the general population of pregnant women. Of 15 confirmed pregnancies reported by Backman et al., 2004 that occurred with the LNG 52 mg IUS *in situ*, 8 (53%, 95% CI 28, 79%) ended in miscarriage. Of the 5 pregnancies reported by Andersson et al., 1994, 2 (40%, 95% CI 0, 83%) ended in miscarriage. One of these women became pregnant with the LNG IUS *in situ* and the other became pregnant after an unrecognized

expulsion. [redacted]

7.1.3.2 Ectopic Pregnancy

Women who become pregnant while using an LNG IUS can experience an ectopic (extrauterine) pregnancy. Overall, the risk of a woman having an ectopic pregnancy is lower than the general population because the risk of pregnancy is significantly decreased. [redacted]

7.1.3.3 Effects on gestation and offspring

When pregnancy continues with the LNG20 IUS in place, the risks of long-term effects on the offspring are unknown. Based on data from copper IUDs, pregnancies that continue are at an increased risk of pre-term (<37 weeks) delivery as compared to women who conceive without an IUD in place (Ganer et al., 2009). The risk is highest if the IUD is not removed (18%) as compared to if the IUD is removed (14%); the risk in the general population is around 7%. Additionally, pregnancies that continue are also at a higher risk of being complicated by chorioamnionitis; 7% if the IUD remains, 4% if the IUD is removed, and slightly less than 1% in the general population (Ganer et al., 2009). It is unknown whether these risks are similar for women who conceive while using a LNG IUS.

7.1.4 Difficult Insertion/Removal

[redacted]

[redacted]

Management of difficult insertion and removal are outlined in Appendix G.

7.1.5 Expulsion

[redacted]

The expulsion rate in the first year in women using a LNG 52 mg IUS for HMB is approximately the same (3.9%) (Mawet et al., 2014). Expulsion management is outlined in Appendix G.

7.1.6 Pelvic Infection

[redacted] Pelvic infection management is outlined in Appendix G.

7.1.7 Perforation

The incidence of uterine perforation during a LNG20 IUS placement attempt in the M360-L102 study is 0.1% (Eisenberg et al., 2015). Perforation management is outlined in Appendix G.

7.1.8 Pelvic/Abdominal Pain

Some women experience pelvic pain or cramping with insertion and a small percentage notice continued or intermittent pain with continued use of LNG20 IUS. Pain may be due to uterine cramping (perhaps related to placement or the presence of the IUS) or functional ovarian cysts. However, there is no clear data on whether the incidence of functional ovarian cysts is increased in LNG20 IUS users as compared to the general population. In the M360-L102, ovarian cysts over multiple years of use are reported in 4.5% of women and discontinuation for ovarian functional cysts occurred in only 0.3% (Teal et al., 2019).

7.1.9 Systemic Side Effects

Although systemic levonorgestrel levels are very low, women using LNG20 IUS do report progestin-related side effects, albeit at low rates. Use of a LNG IUS may affect glucose tolerance; subjects with diabetes should continue routine monitoring of blood glucose concentration with their diabetes care provider.

7.1.10 Mortality

The risk of death with IUD use ranges from 1 to 6 per million users per year. This rate is lower than all other female methods of contraception and lower than use of no contraception when considering the risk of pregnancy (Harlap et al., 1991).

7.1.11 Missing Strings

Rarely, the IUS strings may not be visible during a speculum examination. The IUS is most typically in the uterus when strings are missing. However, the strings could be missing because of a perforation or expulsion. Missing string management, including appropriate imaging to determine the location of the IUS, is outlined in Appendix G.

7.1.12 Phlebotomy

There is an infrequent chance of pain, bruising, or bleeding at the site of the needle puncture, and a rare chance of fainting, inflammation of the vein, or infection.

7.1.13 Pelvic Examination

The subject may infrequently experience some discomfort during the pelvic exams, Pap test, and Chlamydia and gonorrhea testing. Any reaction would most likely include redness, itching, irritation, or vulvovaginal discomfort. Infrequently the subject may have a small amount of vaginal bleeding after a Pap test, Chlamydia or gonorrhea testing.

7.1.14 Endometrial Biopsy

An endometrial biopsy commonly causes light bleeding the day of the procedure and uterine/pelvic cramping for a few minutes, primarily during the procedure. Rarely, a biopsy can result in infection or uterine perforation.

7.1.15 Vaginal Ultrasound

A formal vaginal ultrasound examination will be performed for women at screening (if not performed within the last 6 months), if a subject has missing IUS strings, if a subject becomes pregnant, and for other indications that would clinically require such an examination. Typically, the subject may feel mild discomfort similar to a pelvic examination.

7.1.16 Local Anesthesia

If the clinician uses cervical anesthesia during insertion or removal, there is an infrequent risk of the subject experiencing an unusual taste in her mouth, ringing in her ears, nausea or light-headedness. Rarely, a seizure or death can occur.

7.1.17 Emotional Discomfort

Some of the questions asked in this study may make the subject feel uncomfortable or embarrassed. A subject can refuse to answer any question that causes emotional discomfort, from any person, at any time.

7.2 Overall Assessment of Benefits and Risks

All available information supports a favorable risk-benefit ratio.

7.3 General Plan to Manage Safety

The safety profile of currently available IUSs, as reported during clinical trials and since marketing approval, has been well-characterized. Adverse events that have been reported in relation to IUS use, such as expulsion, vaginal bleeding, uterus perforation, and infection will be specifically monitored. Serious Adverse Events will be reported as per FDA guidance.

7.4 Pregnancy Assessment and Reporting

High sensitivity urine pregnancy tests are performed at each study visit. For any positive pregnancy test on IUS treatment through Visit 8/Early Discontinuation:

- Immediately obtain a serum quantitative hCG
- Within 3 calendar days conduct a transvaginal ultrasound for pregnancy confirmation, pregnancy location and date of conception
    - If the pregnancy is too early for ultrasound verification have the subject return in approximately 1-2 weeks for an unscheduled visit and repeat ultrasound examination
- Complete a Pregnancy Narrative (See Study Reference Manual)

If the subject reports a positive pregnancy test on her own (performed at home) she should be seen as soon as possible for a high-sensitivity urine pregnancy test to be performed at the clinic and if the test is positive perform the required procedures above.

For pregnancies occurring before IUS discontinuation, ultrasonography will also be used to verify presence of the IUS in the uterus.

All confirmed pregnancies occurring during study treatment will be followed to completion. Pregnancy outcomes, including normal births, septic abortions, ectopic pregnancies, birth defects, and premature deliveries, whenever this information is available, will be obtained. Pregnancy reporting should include a Pregnancy Report Form Case Report Form (CRF) and Pregnancy Outcome CRF.

Pregnancy management is outlined in Appendix F.

7.5 Adverse Events Assessments

During the study, the Investigator or study site personnel will be responsible for querying and recording adverse events (AEs) and serious adverse events (SAEs), as detailed below. For the Sponsor to fulfill safety assessment obligations the Investigator should report all SAEs resulting from study participation (e.g., complications resulting from a study-required procedure, such as the taking of a blood sample).

7.6 Definition of an Adverse Event

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. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

- Any medical condition or clinically significant laboratory abnormality with an onset before the study IUS insertion is considered to be pre-existing and should not be documented in the CRF as an AE, but should be recorded as medical history.
- Any AE (i.e., a new event or an exacerbation of a pre-existing condition) with an onset from the beginning of study IUS insertion through Visit 8/Early Discontinuation and the post-Treatment Phase safety contact (if applicable) should be recorded.
- All AEs must be recorded regardless of the severity or relationship to study medication.
- All AEs that result in permanent discontinuation of the investigational product must be reported, whether serious or non-serious.
- An AE **does** include:
    - exacerbation of a pre-existing illness
    - increase in frequency or intensity of a pre-existing episodic event or condition
    - condition occurring after study IUS insertion
    - continuous persistent disease or symptoms present at baseline that worsen following the start of the study
- An AE **does not** include:
    - medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure may be an adverse event if the condition has worsened since enrolling in the study

- pre-existing diseases or conditions present or detected prior to start of study drug administration that do not worsen
- situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- disease or disorder being studied or sign or symptom associated with that disease
- overdose of concomitant medication without any signs or symptoms

7.7 Definition of a Serious Adverse Event

A **serious adverse event (SAE)** is any adverse event occurring within the timelines specified in the protocol that results in any of the following outcomes:

- Death
- Life-threatening situation
  - The subject was at immediate risk of death from the event as it occurred
  - Does not include an event that might have led to death, if it had occurred with greater severity
- Inpatient hospitalization or prolongation of existing hospitalization
  - Does not require inclusion of elective surgery; however, any adverse event occurring during that hospitalization that prolongs the hospital stay would be an SAE
  - Does not have a requirement to be greater than a twenty-four hour stay; if the subject was admitted to the hospital for less than a day for treatment or observation, the definition of "Inpatient hospitalization" is met
  - Treatment in an outpatient clinic or Emergency department does not constitute "inpatient hospitalization"
  - Complications that occur during hospitalizations are AEs; if a complication prolongs hospitalization, it is an SAE
- 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. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

7.8 Prompt Reporting of SAEs to Sponsor

The Sponsor has requirements for reporting serious adverse events to regulatory agencies for a drug under clinical investigation. The Sponsor must be notified within **24 hours of discovery** and the Investigator determines that an adverse event meets the protocol definition of an SAE. Any fatal or life-threatening events should be reported immediately by telephone to the Sponsor. All SAEs occurring from the beginning of study screening through Visit 8/Early Discontinuation and the post-Treatment Phase safety contact (if applicable) require reporting to the Sponsor. Investigators should not wait to receive additional information to fully document the event prior to notifying the Sponsor but should provide as much relevant information as immediately available. Further details of the event can be provided as they become available. The procedures for reporting SAEs are in the Study Reference Manual.

- It is very important that the Investigator provides an assessment of the causal relationship between the event and the study drug at the time of the initial report (see 7.10.2 for Causality definitions)
- The Investigator, or responsible person according to local requirements, must comply with the applicable local regulatory requirements concerning the reporting of SAEs to regulatory authorities and the IRB

7.9 Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events and Serious Adverse Events

Abnormal laboratory findings (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g., X-rays, vital signs) per se are not reported as AEs. However, abnormal findings that are deemed **clinically significant** (i.e., associated with signs and/or symptoms or requiring therapeutic intervention) must be recorded as AEs if they meet the definition of an

adverse event (and recorded as an SAE if they meet the criteria of being serious) as described previously. Clinically significant abnormal laboratory or other abnormal findings that are detected after IUS insertion or that are present at baseline and worsen following study IUS insertion are included as AEs (and SAEs if serious).

The Investigator should exercise his or her medical judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. A clinically significant laboratory abnormality in the absence of clinical symptoms may also jeopardize the subject and may require intervention to prevent immediate consequences (e.g., a markedly high serum potassium concentration may not be accompanied by arrhythmia, yet be of a magnitude to require potassium-binding resin administration to prevent such sequelae). Subjects should undergo repeat testing of clinically significant abnormal laboratory findings as soon as they are recognized.

7.10 Reporting of Adverse Events

Any AE with an onset after study IUS insertion or until the final safety contact after study discontinuation must be documented in the subject's study records and appropriate CRF.

7.10.1 Adverse Event CRFs

Specific Adverse Events are recorded on different CRFs.
AEs related to bleeding or cramping/pain

- With insertion - report on the IUS Insertion Questionnaire CRF
- With removal - report on the IUS Removal Questionnaire CRF
- During IUS use
    - The subject's diary acts as the menstrual bleeding or cramping/pain AE CRF
        - Menstrual bleeding or cramping/pain should also be reported on the general AE CRF only if:
            - Bleeding or cramping/pain are not related to the IUS or a menstrual condition

- 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 and cramping event terminology-consistent use of adverse event terminology is essential for characterization of the product:
  - Heavy menstrual bleeding (increase in flow worse than baseline)
  - Irregular bleeding (variation in bleeding pattern)
  - Infrequent bleeding (bleeding episodes that are too rare)
  - Amenorrhea (no bleeding or spotting)
  - Frequent bleeding (too many bleeding/spotting episodes)
  - Prolonged bleeding (persistent bleeding/spotting)

7.10.2 Causality Assessment: Adverse Event Relationship

The Investigator's causality assessment should consider the potential etiologies for the observed adverse event. An adverse event may be related to the study drug, other concomitant medications, the underlying disease pathology, intercurrent illness, a procedure performed in the course of the study, or another reason. Among the potential etiologies, the Investigator should make a determination based on the most likely causal relationship. When a causality assessment is provided for a serious adverse event, it is important to include a rationale for the assessment so that a better understanding of the reported event can be compiled. The rationale should be accompanied by all available supporting evidence, including relevant laboratory tests, histopathology evaluations and the results of other diagnostic procedures. The Investigator's rationale with supporting evidence is valuable when the Sponsor performs a cumulative analysis of similar events.

The Investigator will assess the relationship of the AE to the study IUS or the IUS insertion or removal procedures by using the following general guidelines:

- **Not Related**: A causal relationship between the study IUS/procedures and the AE can be ruled out (e.g., based on the temporal sequence, absence of a reasonable pathophysiological mechanism, or direct evidence of actual cause).
- **Unlikely related**: A clinical event, including a laboratory test abnormality, with a temporal relationship to IUS insertion or the onset of an IUS insertion or removal procedure which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
- **Probably Related**: A clinical event, including a laboratory test abnormality, with a reasonable time sequence to IUS insertion or the onset of an IUS insertion or removal procedure, unlikely to be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Related:** A clinical event, including a laboratory test abnormality, with a reasonable time sequence to IUS insertion or the onset of an IUS insertion or removal procedure, cannot be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal.

7.10.3 Adverse Event Severity

The Investigator will assess the severity of the AE using the following general guidelines:

- **Mild:** An AE that is usually transient, requiring no special treatment, and does not interfere with the subject's daily activities
- **Moderate**: An AE that introduces a low level of inconvenience or concern to the subject and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures
- **Severe**: An AE that interrupts a subject's usually daily activity and typically requires systemic drug therapy or other treatment (a severe AE may not necessarily qualify as a SAE)
- **Life-threatening**: An AE that put the subject at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.

7.10.4 Adverse Event Outcome

The Investigator will categorize the outcome of each Adverse Event according to the definitions below:

- **Resolved:** The subject recovered from the AE
- **Resolved with sequelae / Stable**: A condition whereby the consequences of a disease or injury include lingering effects that are not worsening
- **Ongoing:** At the time of the last assessment, the event is ongoing, with an undetermined outcome. Note: Ongoing AEs are not considered resolved as a result of death and no AE stop date should be recorded for an AE that is ongoing at the time of death.
- **Fatal:** Adverse Event directly caused death. The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a subject dies during participation in the study or during a recognized follow-up period, the Sponsor should be provided with a copy of any post-mortem findings, including histopathology.
- **Unknown:** The outcome is not known and cannot otherwise be categorized (e.g., subject became lost to follow-up (LTFU) or withdrew consent)

The Investigator should attempt to establish a diagnosis of the event based on the signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE (and SAE if serious) and not the individual signs/symptoms.
In the case of abnormal labs or diagnostic tests judged to be clinically significant by the Investigator a diagnosis, if known, or clinical signs or symptoms if the diagnosis is unknown, rather than the clinically significant laboratory finding or abnormal assessment, should be used to complete the AE/SAE page. If no diagnosis is known and clinical signs or symptoms are not present, then the abnormal finding should be recorded on the AE/SAE page. If an SAE report is completed, pertinent laboratory data should be recorded on the SAE form, preferably with baseline values and copies of laboratory reports.

7.11 Clarification of Action Taken with IUS

The Investigator will categorize the Action Taken with IUS according to the definitions below:

- **None:** The IUS was not removed as result of the Adverse Event

  - IUS was left in place
  - IUS was removed at the time of the AE but due to:
    - A different AE
    - A different reason
    - The subject wanting the IUS removed because of the AE despite the investigator stating the AE was not a reason to have the IUS removed
  - IUS was already removed prior to the AE start date
  - AE was a full expulsion
  - subject was LTFU or withdrew consent prior to IUS removal
- **IUS Removed for Non-Safety Reasons**: The IUS was removed for an Adverse Event even though the IUS could have remained in place without placing the subject at immediate risk for a serious complication related to the IUS
- **IUS Removed for Safety Reasons**: The IUS was removed for an Adverse Event because the subject was at immediate risk for a serious complication as a direct result of the AE if the IUS had not been removed
- **Unknown**: The IUS was removed by another provider

7.12 Clarification of "Other Action Taken"

The investigator will indicate the specific treatment provided as a result of the Adverse Event (this does not include diagnostic tests or referrals).

7.13 Clarification of Adverse Events Related to Study Procedures

Any untoward event that occurs from the beginning of the IUS insertion procedure until completion of insertion, or from the beginning of the removal procedure until the completion of removal, will be reported as an AE. Bleeding and cramping/pain occurring during IUS insertion or removal will be recorded on the IUS Insertion and Removal CRFs, as appropriate. Any other insertion or removal AEs should be recorded on the AE CRF with a causality assessment of "related to IUS procedure." If any AE meets the definition of a Serious Adverse Event, even if it is recorded on the diary or Insertion or Removal CRF, it should also be reported on the AE and SAE CRFs and submitted to Sponsor.

7.14 Follow-up of Adverse Events and Serious Adverse Events

All AEs and SAEs must be followed through the Safety Follow-up, and any IUS or IUS procedure related AEs or SAEs followed until resolution, or until the condition stabilizes, or until all queries are resolved, or until the subject dies or is lost to follow-up (including withdrawal of consent). The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE/SAE. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals. Follow-up information should be submitted to the Sponsor in a timely many as the information is obtained.

7.15 Clarification in Reporting of Deaths

All subject deaths (regardless of relationship to study drug) should be reported that occur from the signing informed consent through declaring the subject as a screen failure or Visit 8/Early Discontinuation and the post-Treatment Phase safety contact (if applicable). The information should be recorded on the Subject Death form and the SAE form.

Death is an outcome of an adverse event and not an adverse event itself. All reports of subject death should include an adverse event term (other than "death") for the cause of the death. Since reporting of an SAE is required within 24 hours of discovery, death can be reported as an initial event term and updated to the final diagnosis in a follow-up report. If an adverse event term is not provided, the Investigator will be queried to obtain the cause of death. Only in the rare occurrence that no verbatim description of an adverse event can be obtained from the investigative site will "Death – Unknown Cause" be used as the event term.

7.16 Post-Study Treatment Reporting Requirements

For all enrolled subjects, all AEs and SAEs, regardless of cause or relationship that occur from IUS discontinuation through the Safety Follow-up require reporting to the Sponsor. In addition, if the Investigator learns of any SAE at any time after a subject has discontinued study drug, and such event seems reasonably related to study drug, the Investigator should promptly notify the Sponsor.

7.17 Subject Withdrawal

7.17.1 Criteria for Withdrawal of Subject from Treatment

The following criteria will be used to determine when a subject should be withdrawn from treatment (removal of study IUS):

- Subjects may choose to discontinue IUS use at any time during the study
- Subjects who become pregnant during study participation will have the IUS removed
    - Subjects who become pregnant during study treatment will continue to be followed until pregnancy completion or termination to determine health-related outcomes of the pregnancy
    - The Investigator will provide pregnancy outcome information as a follow up to the initial pregnancy reporting form
- When IUS perforation occurs during insertion or while on treatment, the IUS will be removed and the subject will be discontinued
- Subjects who experience an IUS expulsion (partial or complete) unless a second study IUS can be inserted within 2 weeks (one-time only) and reinsertion occurs at least 7 days prior to and not during either treatment Cycle 3 or Cycle 6
- The Investigator or Sponsor may discontinue a subject from treatment for other reasons. These may include, but are not limited to, the following:
    - Noncompliance with return visit schedule, diary completion, or use of an excluded therapy
    - A clinically significant IUS-related adverse event or the development of a new significant medical condition that compromises the subject's ability to participate in the study
    - Determination that it is not in the subject's best interest to continue treatment

7.17.2 Withdrawal from the Study

The following criteria will be used to determine when a subject should be withdrawn from the study:

- A subject may withdraw consent for further participation in the study at any time without giving a reason

- A subject may choose to stop participation in the study for any reason. If the subject has not withdrawn consent and has an IUS in place they should be brought in for IUS removal and have appropriate safety follow-up procedures.
- A subject may also be discontinued from the study at the request of the Investigator or the Sponsor. If the subject has an IUS in place they should be brought in for removal and have appropriate safety follow-up procedures.
- Sponsor decision to terminate the study or discontinue the investigative site's participation

Reasons for subject withdrawal from the study should be documented in the subject's file and entered into the CRF.

Subjects that are designated as withdrawn from the study, lost to follow-up or who withdraw consent may not re-enter the study and no further data collection will occur.

7.17.3 Screen Failures

A Screen Failure is defined as any subject that has given consent to participate in the study (i.e. signed an Informed Consent Form) and subsequently was not enrolled for IUS insertion.

7.17.4 Missed Visits/Contacts and Lost to Follow Up

All reasonable efforts should be made to ensure that subjects in screening and enrolled subjects return to the investigational site for all study visits. Once a subject is designated as lost to follow-up, no additional information is to be obtained on any outcomes and no further study-related activities are to be conducted, even if the subject later resumes contact.

7.17.4.1 During Screening

Any subject who misses a scheduled visit should have further contact attempts by the study staff as follows:

- At least three documented attempts to contact the subject by phone, e-mail or similar mode of communication

- If the subject cannot be contacted, or is contacted and still fails to come in for a scheduled visit, a certified letter must be sent to the subject indicating that she will be considered a screen failure (lost to follow-up) and cannot continue in the study

7.17.4.2 After Enrollment

Any subject who misses a scheduled visit should have further contact attempts by the study staff as follows:

- At least three documented attempts to contact the subject by phone, e-mail or similar mode of communication
- If the subject cannot be contacted, or is contacted and still fails to come in for a scheduled visit, a certified letter must be sent to the subject indicating the importance of follow-up and instructed to contact the site immediately
- If subject contact for either a missed Visit 6 or Visit 7 is unsuccessful then future attempts should be made at the time of the next expected study visit
    - At least three documented attempts to contact the subject by phone, e-mail or similar mode of communication should be completed
    - If the subject cannot be contacted or is successfully contacted but still fails to be seen for a scheduled study visit, a certified letter must be sent to the subject indicating the importance of follow-up and should be instructed to contact the site immediately. The letter should indicate that failure to reply within 30 days of the letter date will result in study discontinuation and no future study-related activities will be provided. Certified letters do not need to be sent for subsequent missed study visits if a previous delivery attempt was unsuccessful (letter returned or accepted with no subsequent response).

A subject should be considered lost to follow-up when:

- A subject in the Treatment Phase does not report for V8
- The safety follow-up contact (if applicable) is missed and three documented contacts and a certified letter do not result in subject contact within 14 days of the end of the expected contact window

7.17.5 Withdrawal of Consent

Subjects expressing a desire to withdraw consent for participation in this study should have no further study-related activities conducted. It is preferable that a subject documents her withdrawal of consent in writing.

8. DATA QUALITY CONTROL AND ASSURANCE

Electronic Case Report Forms (eCRFs) for this study will be designed and provided by [redacted] eCRFs will be completed by authorized study staff at each study location and transmitted to [redacted] Daily diary entries by the subject will be entered into an eCRF by site staff. [redacted] will be responsible for data management of this trial, including quality checking of CRFs. In the event of incomplete or inconsistent data, requests for data correction will be sent to the sites for resolution. A complete audit trail of changes to the data will be maintained and available from the clinical trial database. Laboratory data (e.g., hemoglobin/hematocrit, ferritin, chemistry, quantitative hCG, urine pregnancy, Chlamydia, gonorrhea, FSH, TSH, PRL, vWF, ALT, AST) will be collected utilizing the site's local accredited laboratory (unless performing CLIA-waived tests). The site will enter the laboratory values for subjects in the clinical trial electronic database. The Data Management Plan will describe the quality checks that will be performed on the CRFs and the electronic data. CRFs and correction documentation will be converted to pdf format and bookmarked for indexing. Records retention for study data will be consistent with [redacted] standard procedures. Routine system backup and archiving will also be performed based on [redacted] standard procedures.

This study will be conducted in accordance with all applicable FDA guidances and regulations.

9. PLANNED STATISTICAL METHODS

The following statistical methods will be used to assess the efficacy and safety of LNG20 IUS for the treatment of HMB. Prior to implementing the analysis a detailed statistical analysis plan will be written.

9.1 Sample Size

Eligible subjects 18-50 years of age will include approximately 100 subjects using LNG20 IUS. The sample size estimate 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 85 will provide at least 71.5% 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 will provide sufficient number of subjects, for the goal of approximately 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.

9.2 Analysis Populations

The following subject populations will be created:

- Safety (Safety): All subjects enrolled who underwent the IUS insertion procedure, regardless of outcome.
- Modified-Intent-To-Treat (MITT): All subjects at study entry for whom the IUS is successfully placed in the uterus with valid baseline data and for whom there is at least one assessment of MBL during the treatment phase.
- Per Protocol (PP): A subset of the MITT population that excludes subjects with major protocol deviations (to be identified prior to data lock).

9.3 Disposition of Subjects

The number of subjects, who are enrolled, receive an IUS, are discontinued due to failed IUS insertion, have an IUS removal or expulsion, completed each scheduled study visit and who complete the study will be summarized.

9.4 Demographic and Other Subject Characteristics

Subject demographics and pre-treatment characteristics will be summarized.

9.5 Extent of Exposure

Exposure to study IUS will be summarized by treatment duration.

9.6 Pre-trial and Concomitant Medications

Concomitant medications include any medication or health product (any prescription medications or over-the-counter preparations) taken during the screening phase through the active study treatment phase. Pre-trial medications include any medications taken within seven days (30 days for anticoagulants) of Screening Visit 1. The number and percentage of subjects using medications, as captured on the Concomitant Medication CRF form, will be tabulated according to the medication's World Health Organization Anatomical Therapeutic Drug Class and Generic Name by treatment group and overall. Pre-trial and concomitant medications will be presented separately.

9.7 Primary Outcome

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 6 months (during the sixth 28-day cycle) after initial LNG20 IUS insertion. This outcome will be established in the Modified-Intent-To-Treat (MITT) population measuring the change in absolute value from baseline MBL to the end of treatment MBL. Baseline MBL is the MBL averaged over each of the cycles measured during the Screening Phase. 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

The primary outcome measure will be analyzed with 95% confidence interval based on normal approximation. The efficacy of LNG20 IUS for the treatment of heavy menstrual bleeding will be established in this study if the lower bound of the 95% confidence interval equals or exceeds 70%.

9.8 Key Secondary Outcomes

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.

- 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)
- Percent change from baseline MBL to end of treatment MBL (Cycle 6)
- 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) in the number of days of bleeding, spotting, bleeding and spotting and number of bleeding episodes

9.9 Other Secondary Outcomes

All other secondary outcomes will be analyzed using the Safety Population unless noted otherwise.

- Percent change in hemoglobin, hematocrit and serum ferritin from baseline to mid-treatment (Visit 7), from baseline to end of treatment (Visit 8) and from mid-treatment (Visit 7) to end of treatment (Visit 8)
- Continuation rate during Treatment Phase
- Cumulative IUS continuation rates at Treatment Phase Visit 6, Visit 7 and Visit 8 will be summarized using Kaplan-Meier methods
- Adverse events

  The number and percentage of subjects with each adverse event and serious adverse event will be presented by MedDRA system organ class, preferred term, and treatment group.

Summaries will also be presented by relationship to the type of IUS or IUS insertion or removal procedure and the severity of the adverse event. All adverse events will be summarized with special attention to those events that may be related to an IUS, including:

- Perforation of the uterus;
- Low abdominal pain (not classified as dysmenorrhea);
- Uterine infection (including PID); and
- Other urogenital infections

- IUS Expulsion Rates
  - Cumulative IUS expulsion rates at Treatment Phase Visit 6, Visit 7 and Visit 8 will be summarized using Kaplan-Meier methods
- IUS Safety-Related Removal Rates
  - Cumulative IUS safety-related removal rates at Treatment Phase Visit 6, Visit 7 and Visit 8 will be summarized using Kaplan-Meier methods
- Vaginal Bleeding Flow
  - Vaginal bleeding flow (none, spotting, and light, normal, or heavy flow [bleeding]) will be summarized by incidence and duration of bleeding. Vaginal bleeding is recorded on the daily diary during the Screening Phase and baseline will be considered 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 (for women who use mini pads for daily protection, extra protection is not required); if spotting and bleeding occur on the same day, it is recorded as a bleeding day
  - 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 defines 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 (defined as not requiring sanitary protection except for panty liners)
- 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 cycles.

- Dysmenorrhea

  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 and the last 90-day interval after enrollment through IUS Discontinuation. In addition, dysmenorrhea changes from baseline (as established by the worst cramping during the screening cycles) will be summarized using shift tables.
- Other Outcomes

  Changes in other outcomes such as physical exam, vital signs and pelvic exam, will be summarized using descriptive statistics as appropriate.

9.10 Study Stopping Rules Based on Safety

The study will be stopped if safety issues arise that are inconsistent with the medical and scientific understanding of the expected benefits of treatment with a LNG 52 mg IUS in women with HMB.

10. ADMINISTRATIVE CONSIDERATIONS

10.1 Ethical Considerations

All subjects will be counseled that IUS use does not protect against HIV infection or other sexually transmitted infections (STIs). If a subject feels she is at risk of contracting a sexually transmitted

infection, she will be advised to use a male condom until the risk abates. If a subject becomes HIV positive or contracts a sexually transmitted infection during the course of the study, the subject will be treated or referred for treatment and, as appropriate, referred to counseling services per CDC guidelines.

10.2 Administrative Structure

This trial will be sponsored by Medicines360 and managed with [redacted] Approximately 30 sites in the U.S. will participate in this study to enroll approximately 100 subjects.

10.3 Responsibilities

10.3.1 Good Clinical Practice

The Investigator and Sponsor will ensure that this study is conducted in full compliance with "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, South Africa, Edinburgh and clarified in Washington and Tokyo), International Conference on Harmonisation (ICH) guidelines, and all applicable FDA guidances and regulations.

10.3.2 Institutional Review Board (IRB) Approval

The protocol, informed consent form and Investigator's Brochure must be submitted to the appropriate IRB for the investigative site. The investigative site should use the central IRB if that site has no local IRB or if the institutional IRB has a reliance agreement with the central IRB. The protocol and informed consent form for this study must be approved in writing by the IRB in accordance with current FDA and local regulations prior to any subject being consented or enrolled in this study at that site.

The Investigator is responsible for obtaining continued review of the clinical research as specified by the responsible IRB. The Investigator must supply Sponsor or designee with written documentation of continued review of the clinical research. All advertisements must be reviewed and approved by the IRB prior to use.

The Investigator is responsible for reporting the following to the IRB:

- Significant findings that become known in the course of the study that might affect the willingness of subjects to continue to participate (e.g., revised Investigator's Brochure, safety reports);
- Protocol and consent amendments prior to implementing the change;
- Notification of study completion or termination.

10.3.3 Informed Consent

Voluntary informed consent will be obtained from all subjects, or the legally authorized representative of the subject participating in this study, in accordance with FDA regulations. The subject's informed consent must be obtained in writing prior to performance of any study-specific activity. The informed consent form used to consent the subject must be approved by both the reviewing IRB and by the Sponsor. The original signed consent form shall be maintained in the subject's study file.

All subjects must be consented utilizing the most current approved version of the informed consent form, and re-consented if required by the IRB for any protocol amendments, or in the event that significant safety information is released by the Sponsor during the course of the trial. A revised consent document must be signed by subjects active in study follow-up only if required by the IRB. Once the IRB approved revised ICF becomes available, the updated consent should be signed, generally at the next scheduled study visit, or sooner if required by the IRB.

The principles of informed consent must be followed to be in compliance with health authorities' regulations for the conduct and monitoring of clinical investigations.

10.3.4 Confidentiality

The Investigator must ensure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials and an identification code (i.e., not names) should be recorded on any form submitted to the Sponsor and IRB.

The Investigator agrees that all information contained in this protocol and information related to the study drug, including but not limited to the Investigator's Brochure, this protocol, CRFs, the

study drug, and any other study information, remain the sole and exclusive property of the Sponsor. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study, regulatory authority or health authority inspectors, or as required by law) without prior written authorization from the Sponsor. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

10.3.5 Study Files and Retention of Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories: (1) Investigator's study file, and (2) subject clinical source documents.

The Investigator's study file will contain the protocol, any amendment or administrative change letter, IRB approvals with correspondence, informed consent forms, drug records, clinic records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence, as per FDA regulations.

Subject clinical source documents include, but are not limited to, the subject's progress notes, laboratory reports, daily diaries and correspondence.

All clinical study documents must be retained by the Investigator for at least 10 years or at least 2 years after the last approval of a marketing application and until there are no pending marketing applications or if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements or request by the Sponsor. The Investigator must notify the Sponsor prior to destroying any clinical study records.

Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to

store these outside of the site so that they can be returned to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

10.3.6 Case Report Forms and Record Maintenance

eCRFs will be supplied by the Sponsor or designated representative and should be handled in accordance with instructions from the Sponsor. The CRFs are electronic and data entry performed via secure internet access. All eCRFs should be filled out completely by Investigators or their assigned personnel or other trained study staff. Daily diary entries by the subject will be made directly onto paper source documents and regularly faxed at study clinic visits to [redacted] Data Management and converted into eCRFs. The completed set of eCRFs will be reviewed by the Investigator who will then sign and date the Investigator's Statement of Verification CRF. Each authorized study staff member will receive a unique access account which will indicate individual use. Access accounts will not be shared among study staff.

The FDA regulations require that the Investigator must retain drug accountability logs, financial records, CRFs, subject files, and other source data for at least two years following completion of the entire study and FDA marketing approval of the New Drug Application (NDA), or two years after the Investigational New Drug Application (IND) is withdrawn by Sponsor. In either case, records should not be destroyed without written approval from Sponsor.

Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified.

10.3.7 Drug Accountability

Medicines360, or its designee, will provide drug accountability records for this study for use by the investigative sites. The recipient will acknowledge receipt of all study drug shipments, indicating content and condition. Damaged supplies will be replaced. Accurate records of all study drug received, dispensed to subjects, returned to the Sponsor, or designee, or destroyed at the study site, should be maintained by the site. No study IUS is to be destroyed or returned without authorization from the Sponsor, or designee.

10.3.8 Inspections

The Investigator must ensure that source documents for this study should be made available to appropriately qualified personnel from the Sponsor or designee, or regulatory and health authority inspectors.

10.3.9 Protocol Compliance

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol, and as agreed per their signature on the Protocol Signature Page and Form FDA 1572.

10.3.10 Study Report and Publications

The information obtained through this study will be used by Sponsor in connection with the development of the investigational drug and, therefore, may be used in submission(s) to regulatory authorities. In addition, the results of this study may be used in publications or presented at scientific meetings.

No individual site Investigator or designee will publish, present, or communicate study results without written approval from the Sponsor. After conclusion of the study, Investigators in this study may not communicate orally, present, or publish in scientific journals or other scholarly media any results of this study without prior written approval from the Sponsor. If approval is granted by the Sponsor, the Sponsor maintains the right to review proposed presentations and publications. Investigators will submit to the Sponsor any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days prior to submission of the publication or presentation. The Investigator will comply with any Sponsor or supporter request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

No such communication, presentation, or publication will include the Sponsor's confidential information (see Section 10.3.4).

10.3.11 Investigator Responsibilities

A complete list of Investigator responsibilities are outlined in the clinical study research agreement and the Statement of Investigator Food and Drug Administration (FDA) Form 1572, both of which are signed by the Investigator before commencement of the study. In summary, the Investigator will conduct the study according to the current protocol; will read and understand the Investigator's Brochure; will obtain IRB approval to conduct the study; will obtain informed consent from each study participant; will maintain and supply to the Sponsor or designee, auditors and regulatory agencies adequate and accurate records of study activity and drug accountability for study-related monitoring, audits, IRB reviews and regulatory inspections; will report SAEs to the Sponsor or designee and IRB according to the specifics outlined in this protocol; will personally conduct or supervise the study; and will ensure that colleagues participating in the study are informed about their obligations in meeting the above commitments.

10.3.12 Sponsor Responsibilities

A complete list of the Sponsor responsibilities is outlined in the clinical study research agreement. In summary, the Sponsor will select qualified Investigators, provide them with the information they need to properly conduct the study, ensure adequate monitoring of the study, conduct the study in accordance with the general investigational plan and protocols, and promptly inform Investigators, health and regulatory agencies/authorities as appropriate of significant new adverse effects or risks with respect to the drug.

10.3.13 Protocol Modifications

Changes in any portion of this protocol must be documented in the form of an amendment from the Sponsor and, if required, approved by the site's IRB before the amendment may be implemented at that site. The IRB chairperson may approve minor changes, or may designate one or more regulatory members to approve revisions. Only the most current approved informed consent form should be used when obtaining consent from a new subject.

10.3.14 Access to Information for Monitoring

In accordance with FDA and ICH-GCP guidelines, the study monitor must have direct access to the Investigator's source documentation in order to verify the data recorded on the CRFs for accuracy.

The monitor is responsible for routine review of the CRFs at regular intervals throughout the study, to verify adherence to the protocol, and the completeness, consistency and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRFs. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.3.15 Financial Disclosure

Per Title 21 CFR Part 54, all Investigators will complete a Financial Disclosure Form that permits Sponsor to demonstrate that an Investigator has no personal or professional financial incentive regarding study outcome or the future approval or disapproval of an investigational drug such that the Investigator's research might be biased by such incentive.

10.3.16 Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, both the Sponsor and the Investigator will arrange discontinuation procedures. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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12. APPENDIX A: SCHEDULE OF EVENTS SCREENING

ASSESSMENTS	VISIT 1A	VISIT 1B	VISIT 1C	VISIT 1D	VISIT 1E	VISIT 1F	VISIT 2	VISIT 3	VISIT 4
	SCREENING INITIATION						SCREEN CYCLE 1	SCREEN CYCLE 2	SCREEN CYCLE 3
Informed Consent	X								
Pre-screen Questionnaire	X								
Gynecological and Menstrual History	X								
Medical History	X	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X
Concomitant Medication Review	X	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X
Demographics	X								
Assess history of poor venous access	X								
Confirm Eligibility to this point	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test		X		X	X[3]		X	X	X
Hemoglobin/Hematocrit, Ferritin			X[2]						
FSH, TSH, PRL, vWF, ALT, AST, chemistry (basic metabolic panel)			X[2]						
Blood Pressure/Pulse				X			X	X	X
Weight				X					
Height				X					
Breast Exam				X					
Pelvic Exam				X	X[4]				
Pap test					X[5]				
Gonorrhea/Chlamydia					X[2]		X[7]	X[7]	X[7]
Transvaginal Ultrasound					X[6]				
Endometrial Biopsy					X[6]				
Instruct/Dispense Diaries						X	X	X	X
Instruct/Dispense Sanitary Products						X	X	X	X
Instruct/Dispense Collection Keg						X	X	X	X
Collect Sanitary Products and Collection Keg/Assess for Compliance							X	X	X
Collect Diary/Assess for Compliance							X	X	X
Venous Blood for AH Analysis							X	X	X
Schedule Next Visit/Contact	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X

[1] If visits for part 1 are not done on the same day, perform as needed
[2] If not documented within the last 30 days
[3] Perform urine pregnancy test if this part of Visit 1 is performed on a day different than earlier parts
[4] Only performed as part of endometrial biopsy
[5] Test indicated if no Pap report available indicating no clinical need for testing or follow-up during planned study participation
[6] If not documented within the last 6 months
[7] Test indicated only if change in sexual partner

13. APPENDIX B: SCHEDULE OF EVENTS ENROLLMENT AND FOLLOW-UP

ASSESSMENTS	ENROLLMENT	TREATMENT					7-DAY FU CONTACT[6]	ADDITIONAL FOLLOW-UP[7]
	VISIT 5	VISIT 6	CONTACT	VISIT 7	CONTACT	VISIT 8 or ED		
	IUS INSERT	DAY 28-42	DAY 50-56	DAY 85-89[2]	DAY 133-140	DAY 169-174[2]	7-10 DAYS AFTER IUS REMOVAL	AS NEEDED
Blood Pressure/Pulse	X	X		X		X		
Weight	X	X		X		X		
Medical History	X							
Urine Pregnancy Test	X	X		X		X		
Breast Exam						X		
Pelvic Exam	X					X		
Gonorrhea/Chlamydia	X[1]	X[1]		X[1]		X[1]		
Hemoglobin/Hematocrit, Ferritin	X			X		X[3]		
Venous blood for AH Analysis				X		X		
Confirm Eligibility	X							
Instruct/Dispense Diaries	X	X		X				
Instruct/Dispense Sanitary Products	X	X		X				
Instruct/Dispense Collection Kit		X		X				
Collect Sanitary Products/Collection Kit/Assess for Compliance				X		X		
Collect Diary/Assess for Compliance	X	X		X		X		
VAS Questionnaire	X			X		X		
Insertion of IUS	X							
Review of Adverse Events	X	X		X		X	X	X
Review Concomitant Meds	X	X		X		X	X	X
Verify IUS Presence		X		X		X		
Removal of IUS						X[4]		
Schedule Next Visit/Contact	X	X		X		X[5]		
Remind when to collect Products			X		X			
Confirm Next Visit			X		X			

[1] Test indicated only if change in sexual partner
[2] Visit to occur ideally within the 5 day window but may be up to 21 days (V7 window Days 85-105: V8 window Days 169-189)
[3] If not collected within 6 weeks
[4] As applicable; subject may keep IUS if not contraindicated
[5] If has IUS removed
[6] For subjects with IUS removed
[7] For ongoing IUS or IUS removal-related AEs

14. APPENDIX C: PRE-SCREEN QUESTIONNAIRE

1. Are you 18 to 50 years old?
2. Do you have heavy periods (heavy menstrual bleeding)?
3. Do you have regular (predictable) periods?
4. Have you ever been told you have large uterine fibroids?
5. Do you soak through one or more pads or tampons every hour for several hours?
6. During your typical period do you ever have blood stain your thighs?
7. Do you sometimes use a pad and tampon at the same time?
8. Do you sometimes sleep with a towel between your legs to prevent staining?
9. Do you get up to change your pad/tampon during the night?

Pre-screening Questionnaire Response Requirements:

- May continue screening if meets all of these requirements:
  - Yes to #1, #2 and #3;
  - No to #4;
  - Yes to any one or more questions #5 through #9

15. APPENDIX D: BASELINE VISUAL ANALOG SCALE QUESTIONS

For these questions we are going to ask you to make a mark on a line.

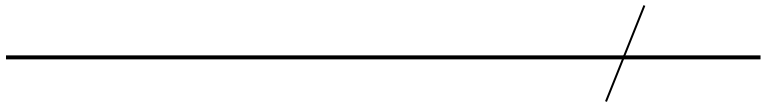
For example, let's say you are asked how much you like Oreo cookies:

How much do you like Oreo cookies? (make a mark on the line)

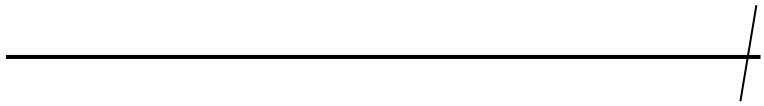
very little ——————————————— very much

You answer the question by making a mark on the line according to how much you like or dislike Oreo cookies.

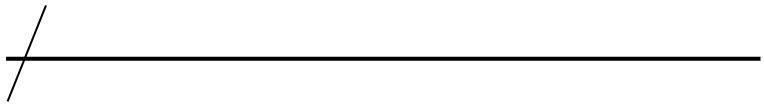
If you liked Oreo cookies a lot, then you might make a mark on the line like so:



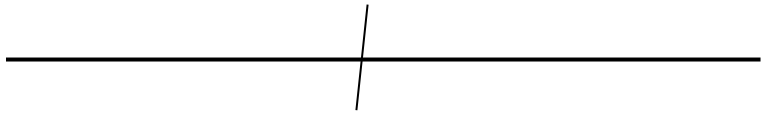
If you liked Oreo cookies more than life itself(!), then you might make a mark on the line like so:



If you hated Oreo cookies, then you might make a mark like so:



If you thought Oreo cookies were just "OK," then you might make a mark like so:



The idea is that if you like Oreo cookies, you make a mark on the line closer to the phrase "very much;" the closer you make the mark, the more you are saying you like Oreo cookies. If you don't like Oreo cookies, you make a mark on the line closer to the phrase "very little;" the closer you make the mark, the more you are saying you don't like Oreo cookies.

PLEASE TURN TO THE NEXT PAGE AND ANSWER THE QUESTIONS.

Make a mark on the line to indicate:

When you think of your <u>typical</u> period, how heavy is your bleeding?

no flow _____ heaviest flow I ever experienced

When you think of your <u>typical</u> period, how acceptable is your bleeding?

not acceptable _____ completely acceptable

When you think of your <u>typical</u> period, how much cramping pain do you have?

no pain _____ worst pain I ever experienced

When you think of your <u>typical</u> period, how much does it interfere with your ability to do daily activities?

no effect _____ I cannot do any daily activities

When you think of your <u>typical</u> period, how much does it affect your ability to sleep?

no effect _____ I do not get any sleep

_____ _____

Date Subject's signature

16. APPENDIX E: 3-MONTH AND 6-MONTH VISUAL ANALOG SCALE QUESTIONS

For these questions we are going to ask you to make a mark on a line.

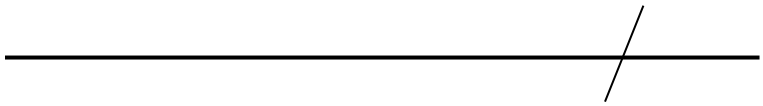
For example, let's say you are asked how much you like Oreo cookies:

How much do you like Oreo cookies? (make a mark on the line)

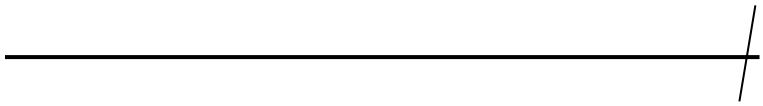
very little ——————————————— very much

You answer the question by making a mark on the line according to how much you like or dislike Oreo cookies.

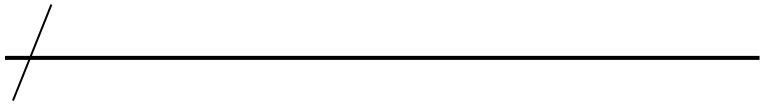
If you liked Oreo cookies a lot, then you might make a mark on the line like so:



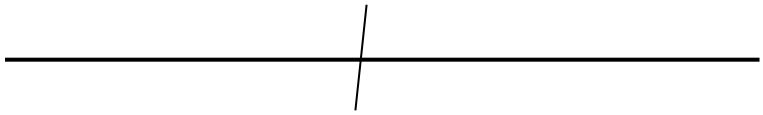
If you liked Oreo cookies more than life itself(!), then you might make a mark on the line like so:



If you hated Oreo cookies, then you might make a mark like so:



If you thought Oreo cookies were just "OK," then you might make a mark like so:



The idea is that if you like Oreo cookies, you make a mark on the line closer to the phrase "very much;" the closer you make the mark, the more you are saying you like Oreo cookies. If you don't like Oreo cookies, you make a mark on the line closer to the phrase "very little;" the closer you make the mark, the more you are saying you don't like Oreo cookies.

PLEASE TURN TO THE NEXT PAGE AND ANSWER THE QUESTIONS.

Make a mark on the line to indicate:

When you think of the bleeding you have had over the last 4 weeks, how heavy was your bleeding?

no flow _____ heaviest flow I ever experienced

When you think of the bleeding you have had over the last 4 weeks, how acceptable was your bleeding?

not acceptable _____ completely acceptable

When you think of the cramping pain you have had over the last 4 weeks, how much cramping pain did you have?

no pain _____ worst pain I ever experienced

When you think of the bleeding and cramping you have had over the last 4 weeks, how much did it interfere with your ability to do daily activities?

no effect _____ I cannot do any daily activities

When you think of the bleeding and cramping you have had over the last 4 weeks, how much did it affect your ability to sleep?

no effect _____ I do not get any sleep

_____ _____

Date **Subject's signature**

17. APPENDIX F: MANAGEMENT OF PREGNANCY

Among women who conceive with an IUS *in situ*, the spontaneous abortion rate is two-fold higher than that of the general obstetric population. A retained IUS also increases the risk of several late gestational adverse maternal and neonatal outcomes; this risk is reduced, but not eliminated, with early removal of the IUS.

For any subject who has a positive urine pregnancy test, the pregnancy should be confirmed by ultrasonography and serum hCG testing. The location of the pregnancy must be determined (intrauterine or extrauterine) using ultrasonography. Determine the location of the IUS using physical examination, ultrasonography and/or radiography as appropriate.

1. Management of intrauterine pregnancy with IUS in place

The following steps may be considered in the evaluation and management of intrauterine pregnancy in a subject with an IUS *in situ*:

- First trimester intrauterine pregnancy:
    - If the IUS strings are visible on speculum examination, remove the IUS to decrease the risk of subsequent miscarriage and infection. Antibiotics are unnecessary.
    - If the strings are not visible and the patient wishes to continue the pregnancy, remove the IUS under ultrasound guidance using an alligator forceps or an IUS hook. Removal can also be attempted by hysteroscopy. Data on hysteroscopic removal of IUS in early pregnancy are limited; therefore, it is not clear whether this technique poses greater or lesser risk of pregnancy loss than instrument removal under ultrasound guidance. Antibiotic prophylaxis is recommended when instrument removals are performed during pregnancy, including when IUS removal is to be followed by pregnancy termination (see below). The IUS may be left *in situ* if findings on ultrasound examination suggest removal will be difficult or disrupt the pregnancy (e.g., IUS embedded in the placenta or membranes).
    - If the woman desires pregnancy termination, IUS removal can be performed at the time of the termination. Manual or electric vacuum aspiration or an instrument such as an IUS hook, alligator forceps, ring forceps, or ovum forceps can be used to remove the IUS.

- In the setting of spontaneous abortion with IUS in place, it is recommended to remove the IUS and prescribe antibiotics (e.g., doxycycline 100 mg twice a day or ampicillin 500 mg four times a day for seven days).

- Second trimester pregnancy —Counsel subject if the IUS remains *in situ*, that there is an increased risk of preterm labor and delivery (fourfold increase), second trimester fetal loss, and infection, but no proven increase in risk of birth defects. Removal of the IUS may cause rupture of membranes, bleeding, pregnancy loss, or fetal trauma; however, if the IUS is removed or expelled without complications, there is no increased risk of miscarriage.
  - Given this information, for pregnancies after 12 weeks, consider removing the IUS by pulling on the strings if the strings are visible and removal is unlikely to disrupt the placenta or membranes (based upon ultrasound localization of the IUS and placenta).
  - If the strings are not visible in the early second trimester, the IUS may be removed under ultrasound guidance if removal appears feasible, the IUS is not located behind the placenta, and it does not appear to be incorporated into the gestational sac. In particular, ultrasound guided removal is recommended in these cases if the IUS is in the lower uterine segment. If the IUS appears embedded in the placenta, located behind the placenta, or protrudes into the gestational sac, we suggest leaving the IUS *in situ*.
  - In the later second trimester, if the strings are not visible, the IUS should be left in place. The subject should be counseled that her risk of spontaneous abortion and premature delivery is increased relative to women whose IUSs may be easily removed.

2. Management of intrauterine pregnancy with extrauterine IUS

- If the IUS was expelled, the pregnancy should be managed as any other intrauterine pregnancy.
- If the IUS is extrauterine (perforation), the pregnancy should be managed without removal of the IUS until after the pregnancy is complete or, if applicable, at the time of cesarean delivery.

3. Management of extrauterine pregnancy

- Management should be performed within the local standard of care for the extrauterine pregnancy.
- If the IUS is intrauterine, the IUS should be removed and the subject discontinued from the study following appropriate safety follow-up.

18. APPENDIX G: MANAGEMENT OF IUS ISSUES

1. Difficult Insertion

If insertion is difficult because the cervix cannot be properly visualized then the subject should have been excluded prior to randomization.

- If insertion is difficult because the uterus cannot be instrumented, the following measures are allowed:
    - Use of cervical anesthesia to make sounding and manipulation more tolerable
    - Use of rigid dilators to dilate the cervix if needed to allow passage of the sound. If needed, a lacrimal duct probe or os finder may be used to start dilation.
    - Abdominal ultrasound guidance during dilation and/or insertion.

  If the uterus still cannot be appropriately instrumented after the above measures are taken, or the uterus sounds to less than 5.5cm, then the subject should be considered an insertion failure and discontinued from the study. No further follow-up or visits are required.

2. Perforation

- Perforation may occur during insertion. The risk of perforation is increased in women with fixed retroverted uteri, during lactation, and postpartum. If during or after insertion there is clinical concern or exceptional pain or bleeding, appropriate and timely measures and assessments, such as ultrasound, should be performed to exclude perforation.
- Perforation or penetration of the uterine wall or cervix may occur during insertion although the perforation may not be detected until sometime later. The IUS must be located and removed; surgery may be required. Delayed detection of perforation may result in migration outside the uterine cavity, adhesions, peritonitis, intestinal perforations, intestinal obstruction, abscesses and erosion of adjacent viscera. Ensure a radiographic image of the entire abdomen is obtained to ensure the IUS hasn't migrated.
- If recognized and the IUS is intra-abdominal, a laparoscopy should be performed by a clinician experienced in such procedures to remove the IUS. Typically, minimal adhesions are present with intra-abdominal IUSs. If necessary, a laparotomy should be performed.

  If the IUS is partially into or through the myometrium, it is reasonable to attempt removal with transcervical instrumentation. Initial attempts should be performed under ultrasound

guidance using an Alligator forceps (or similar instrument). If unsuccessful, attempts via hysteroscopy should be made before proceeding to laparoscopy.

3. Missing Strings

The site should check for the IUS strings by palpation or direct visualization at each study visit. Ultrasound examination to verify the IUS is in place cannot substitute for checking the strings. If the strings are not evident on exam follow these steps, moving to the next one if unsuccessful:

- Use endobrush in cervical canal to attempt to tease down string.
- Perform a transvaginal ultrasound examination to locate the IUS. If the IUS is confirmed to be present in the uterus and the strings are missing, then transvaginal ultrasonography should be performed at all follow-up visits to confirm presence of the IUS.
- Obtain a flat plate abdominal x-ray to check if the IUS is within the abdomen.
    - If it is not visible on abdominal x-ray, the case will be considered a spontaneous expulsion.
    - If it is visible on x-ray, but not within the uterus on ultrasound, the case will be considered a perforation. The patient should then be referred, as necessary, for IUS removal by laparoscopy or laparotomy, and for any other necessary care.
- Subjects who experience IUS expulsion may have another study IUS inserted; only one replacement IUS is allowed per subject. Replacement can occur only if all of the following conditions are met:
    - Reinsertion occurs no more than 14 days after the expulsion;
    - Reinsertion occurs at least 7 days prior to treatment Cycle 3 or Cycle 6;
    - Reinsertion cannot occur during treatment Cycle 3 or Cycle 6;
    - Pregnancy can reasonably be excluded.

4. Partial Expulsion

Defined as visual evidence of the lower portion of the IUS stem protruding through the cervical os OR evidence of increased bleeding and/or cramping complaints with the presence of the IUS in the lower uterine segment. The system can be expelled from the uterine cavity without the woman noticing it, resulting in the loss of contraceptive protection. As menstrual flow typically decreases after the first 3 to 6 months of IUS use, an increase of menstrual flow may be indicative of an expulsion.

- The IUS should be removed as soon as possible.
- Subjects who experience a partial IUS expulsion may have another study IUS inserted (see criteria in #3 above)

5. Infection

- Patients must be taught to recognize and report to their physician promptly any symptoms of pelvic inflammatory disease. These symptoms include development of menstrual disorders (prolonged or heavy bleeding), unusual vaginal discharge, abdominal or pelvic pain or tenderness, dyspareunia, chills, and fever. Following a diagnosis of PID, or suspected PID, bacteriologic specimens should be obtained and antibiotic therapy should be initiated promptly.
- Any woman treated by a medical professional for uterine infection/PID will be considered to have that diagnosis. At a minimum, uterine tenderness must be present. The IUS should not be removed when such a diagnosis is made unless the infection is refractory to antibiotic therapy or the subject has a pelvic abscess or sepsis.

6. Difficult Removal

If the IUS cannot be removed by pulling on the strings, first make sure the clinician is certain the IUS is still in the uterus. Embedment can result in difficult removal and, in some cases surgical removal may be necessary. An embedded IUS should be removed. Embedment may decrease contraceptive effectiveness and result in pregnancy. Once certain the IUS is in the uterus, consider any of the following options alone or in combination:

- Abdominal ultrasound guidance
- Cervical anesthesia to make manipulation more tolerable
- IUD thread retriever
- Alligator forceps (or comparable instrument)

If the IUS still cannot be removed in an office setting using the above techniques, hysteroscopic evaluation for removal should be performed.

After removal of the IUS, verify that the system is intact. If the system is not intact, any missing parts must be located and removed. If removal of missing parts cannot be completed in the office, contact the Medical Monitor before attempting any other procedures. As a reminder, all removed IUSs should be collected and stored in a temperature controlled freezer.

19. APPENDIX H: PROTOCOL SUMMARY OF CHANGES

Any administrative changes to the protocol including spelling corrections, minor clarifications, renumbering, and reformatting are not summarized in the following table. Such changes are evident and may be reviewed in the red-lined Protocol Amendment.

Section	Change to Protocol	Rationale
Title Page, Signature Page	Date and version # changed	The date and version # changed due to this revision
Synopsis Eligibility Criteria and Protocol Section 4.3	Extended Planned study dates Added "approximately" to the Number of Investigative Sites Revised inclusion criterion #10 to add "regardless of subject's age" for screening Pap testing requirements	To allow for a longer enrollment period To allow flexibility in the number of investigative sites To provide clarity
Protocol Sections 3 and 6.7.3.1	Added that the first screening phase cycle analysis may be repeated if the considered less than normal by the subject. The first cycle collection is discarded.	To allow for the variability in bleeding amounts women may experience
Protocol Section 4,2	Revised inclusion criterion #10 to add "regardless of age" for screening Pap testing requirements	To provide clarity
Protocol Section 5.3	Added instruction to contact the sponsor for IUS storage temperature excursions	To ensure quality of the investigational product
Protocol Sections 6	Indicated the flow chart of study assessments has been split into two; one for screening and one for enrollment and follow-up	To provide clarity
Protocol Sections 6.3, 6.7.2.3	Added that screening bloodwork does not require fasting	To provide clarity
Protocol Sections 6.7.1 and 6.7.3.7	Added details about determining if the cycle collection is likely to be less than study requirements before sending feminine hygiene products for analysis	To identify screen failures prior to feminine hygiene product analysis
Protocol Section 7.1.2	Revised to Liletta being approved for contraception for up to 6 years and more current contraceptive efficacy data	FDA approval received 15 October 2019

Protocol Sections 7.1.3.2, 7.1.3.6	Revised ectopic pregnancy rate and pelvic infection occurrence to reflect 6 years of use data	To reflect the current product package insert
Protocol Section 7.10	Revised to indicate collection of AEs to start with study treatment	To be consistent with other sections
Protocol Section 11	Added references	To be current and complete
Appendix A	Schedule of Events now split into Appendix A for screening Added additional assessments	To provide clarity To be more comprehensive