Medicines 360

TITLE PAGE

Title:	A Phase 3, Multi-Center, Open-Label Study of a Levonorgestrel-Releasing Intrauterine System for Long-Term, Reversible Contraception
Test Product:	LNG20 (levonorgestrel-releasing intrauterine system)
IND	105,836
Indication	Intrauterine contraception for up to 10 years in nulliparous and parous women.
Protocol Number:	M360-L102
Investigators	Multi-Center
Development Phase:	Phase 3
Study Design:	Open-Label
Sponsor:	Medicines360
Sponsor's Medical Officer:	[redacted]
Protocol Date:	02 October 2017
Version Number:	Version 9.0 Replaces version 8.0 dated 21 October 2016

CONFIDENTIAL STATEMENT

SIGNATURE PAGE

Clinical Protocol M360-L102

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

Version 9.0
Dated: 02 October 2017

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PROTOCOL SYNOPSIS

Study Title	A Phase 3, Multi-Center, Open-Label Study of a Levonorgestrel-Releasing Intrauterine System for Long-Term, Reversible Contraception
Short Title	LNG20 IUS Phase 3 study for contraception
Study Sponsor	Medicines360
Protocol Number	M360-L102
Study Phase	3
Study Objectives	The primary objective of this study is to assess the efficacy of a levonorgestrel-releasing intrauterine system (LNG20) in nulliparous and parous females of child-bearing potential who request long-term, reversible contraception. The secondary objectives of this study are to assess: • safety, tolerability, bleeding patterns, and continuation rates of LNG20 • return of menses after discontinuation of LNG20 • return to fertility after discontinuation of LNG20 • plasma pharmacokinetics of levonorgestrel in a subset of approximately 60 subjects with serial sampling over the duration of use • plasma levonorgestrel levels in subjects with continuing use from Month 36 through Month 120 • levonorgestrel levels over the first 14 days following removal in a subset of 60 subjects using the LNG20 and completing the entire duration of use • changes in endometrial thickness in a subset of 60 subjects based on transvaginal ultrasonography at 1, 5 and 10 years of LNG20 use • safety and tolerability of LNG20 in a small cohort of women between ages 36 and 45 years for up to 8 years duration of use • analysis of an appropriate sampling of IUSs that are removed and, when available, expelled during the study

Planned Study Dates	Start of study/recruitment: November 2009 End of recruitment: April 2013 End of study treatment: May 2023 End of post-treatment follow-up: May 2024
Number of Investigative Sites	Up to 30 sites in the U.S.
Number of Subjects Planned	Approximately 1,910 women between the ages of 16 and 45 years, inclusive, who request long-term, reversible contraception, provide consent, and satisfy study entry criteria will be enrolled. The sample will include: • approximately 1,760 women between 16 and 35 years of age, inclusive, at enrollment • approximately 150 women between 36 and 45 years of age, inclusive, at enrollment
Study Design	The primary study is a randomized, multi-center, open-label, evaluation of the efficacy of a levonorgestrel-releasing intrauterine system (LNG20). A marketed levonorgestrel-releasing intrauterine system (Mirena®) is included as an informative comparator. Eligible subjects 16-35 years of age will include approximately 1,600 subjects using LNG20 and 160 subjects using Mirena. Approximately 650 LNG20 and 160 Mirena subjects were randomized at a 4:1 ratio of LNG20 to Mirena. However, the remaining 950 subjects will be assigned to LNG20 only. In addition, approximately 150 eligible females 36-45 years old will receive LNG20 as part of a non-randomized cohort. After consent is obtained, screening procedures will be performed and eligible subjects enrolled into the trial via an Interactive Voice Response System (IVRS). The Enrollment Visit and IUS insertion may occur on the same day as the screening procedures. 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 121 months (60

	months for Mirena subjects and 96 months for the LNG20 36-45 year old enrollment group). Study assessments will be performed at a clinic visit at Months 1, 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114, 120 and 121 (Mirena subjects only through Month 60 and the LNG20 36-45 year old enrollment group only through Month 96). Telephone assessments will occur at 3 month intervals between scheduled clinic visits, starting at Month 9. The IUS will be removed when requested, when clinically indicated, or at the end of duration of use which is 121 months for LNG20 subjects, 60 months for Mirena subjects and 96 months for the LNG20 36-45 year old enrollment group. All subjects will have a safety follow-up visit one month after discontinuing study treatment. Additional follow-up will be conducted for subjects who choose a non-hormonal contraceptive method or who indicate they will attempt to become pregnant, as follows: • Those women who elect to start a non-hormonal contraceptive method or no contraception (including those desiring pregnancy) will be followed for return of menses • Those women who desire pregnancy will be followed for up to 12 months following IUS removal or expulsion to document return to fertility Pregnancies will be identified during treatment through subject query and urine pregnancy tests at each scheduled study visit, and after treatment discontinuation (1 month safety follow-up). The date of conception will be estimated by ultrasound examination for pregnancies that occur during study participation. Routine safety monitoring (adverse event assessments and vital signs) will be conducted for all subjects. An Independent Data Monitoring Committee (IDMC) will monitor subject safety throughout study conduct, and will be sent reports of all unexpected related serious adverse events (SAEs) that may occur during the study. The IDMC will review all safety data and make recommendations regarding study conduct.

	Subjects will receive detailed instructions on how to record vaginal bleeding, dysmenorrhea and other contraceptive use in a daily diary and report this information during the first 24 months of study participation. Thereafter, only other contraceptive use will continue to be recorded on a diary by the subject for the remainder of study participation in addition to the information collected at each study visit. After 24 months, bleeding and dysmenorrhea information only will be obtained for the remainder of study participation via interviews by study staff during each study contact (every 3 months) during treatment. Levonorgestrel plasma levels will be obtained for all subjects every 6 months and at IUS discontinuation beginning with Month 36 until Protocol Version 9 when thereafter, levonorgestrel plasma levels will be obtained in all subjects at IUS discontinuation and also annually in all women enrolled prior to 31May2011. The Sponsor intends to retain all IUSs that are removed or expelled (when available) and analyze an appropriate sample of these. The following substudies for women 16-35 years will occur at selected sites: • Levonorgestrel PK data will be generated in a subset of approximately 60 subjects, (20 non-obese LNG20 subjects, 20 non-obese Mirena subjects and 20 obese LNG20 subjects). Blood samples will be obtained at the Enrollment Visit (pre-IUS insertion), Weeks 1 and 2, and Months 1, 3, 6, 9, 12, 18, 24 and 30 after IUS insertion • A subset of 60 women assigned to LNG20 will have transvaginal ultrasound evaluations at Enrollment, Month 12, Month 60 and Month 120 to assess endometrial thickness • A subset of 60 subjects assigned to LNG20 and completing 121 months of study treatment will have levonorgestrel samples obtained at various timepoints after study IUS removal for the characterization of the elimination profile of LNG. Each subject in this subset will be randomized to one timepoint (one extra visit) post-IUS removal (24 hours, 48 hours, 7 days or 14 days) such that fifteen subjects are randomly assigned to each timepoint

Investigational Drugs:	A levonorgestrel-releasing intrauterine system (LNG20) with an initial release rate of approximately 20 mcg/day will be evaluated. A marketed levonorgestrel-releasing intrauterine system (Mirena) with an initial release rate of approximately 20 mcg/day will be included as an informative comparator.
Dosing Regimen:	At study entry, a LNG20 or Mirena will be inserted into the uterus by a study Investigator using standardized procedures specific to each system. The LNG20 will be removed at Month 121 for the 16-35 year old enrollment group and at Month 96 for the LNG20 36-45 year old enrollment group. Mirena will be removed at Month 60. Either IUS may be removed earlier if requested by the subject or judged necessary by the Investigator. Subjects who experience IUS expulsion (partial or complete) will be discontinued from study treatment. An IUS that is expelled during the study will not be replaced with a new LNG20 or Mirena IUS in this study.
Primary Outcome Measure:	Efficacy of LNG20 at 2 years of use. This outcome will be established in the Modified Intent To Treat (MITT) population by calculating the Pearl Indices for use during year 1 and year 2. The Pearl Index for each year must have acceptable precision, defined as the upper bound of the 95% confidence interval being no more than 1 unit above the point estimate.
Key Secondary Outcome Measures:	Efficacy of LNG20 at 3, 4, 5, 6, 7, 8, 9 and 10 years of use. This outcome will be established in the MITT population by calculating the Pearl Indices for use during year 3, year 4, year 5, year 6, year 7, year 8, year 9 and year 10.
Other Secondary Outcome Measures:	Other secondary outcomes that will be assessed for LNG20 and Mirena will include: • Cumulative LNG20 pregnancy rates for years 2 through 10 • IUS continuation rates at 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years

	○ Years 6, 7 and 8 will only include LNG20 subjects ○ Years 9 and 10 will only include the LNG20 16-35 year old enrollment group • IUS expulsion rates at 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years and 10 years ○ Years 6, 7 and 8 will only include LNG20 subjects ○ Years 9 and 10 will only include the LNG20 16-35 year old enrollment group • IUS safety-related removal rates at 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years and 10 years ○ Years 6, 7 and 8 will only include LNG20 subjects ○ Years 9 and 10 will only include the LNG20 16-35 year old enrollment group • Vaginal bleeding patterns during IUS use • Dysmenorrhea during IUS use • Hemoglobin over the duration of IUS use • Adverse events • Pregnancy outcomes • Fertility rates one year following removal of the IUS • Occurrence of menses after IUS discontinuation • Plasma levonorgestrel levels over the duration of IUS use • Analysis of an appropriate sampling of IUSs that are removed or expelled during the study Other secondary outcomes that will be assessed for LNG20 will include: • Plasma levonorgestrel levels over the first 14 days following LNG20 removal after Month 121 • Endometrial thickness at 1, 5 and 10 years of LNG20 use as compared to baseline

Duration of Subject Participation:	LNG20 16-35 year old enrollment group: up to 11 years, 1 month (approximately 133 months) LNG20 36-45 year old enrollment group: up to 9 years, 1 month (approximately 109 months) Mirena group: up to 6 years, 1 month (approximately 73 months)
Duration of Study Center Participation:	Up to 14.7 years from start of study enrollment assuming 3 months for study start-up activities, an enrollment period up to 3 years, up to 10 years and 1 month subject treatment, 1 year pregnancy follow-up and 3 months post-monitoring/query resolution.
Eligibility Criteria:	**Inclusion Criteria** Subjects must fulfill all of the following criteria to be eligible for study entry: 1) Signed informed consent 2) Healthy females 16-45 years of age, inclusive, at the time of enrollment (unemancipated subjects less than 18 years of age must also have written parental consent documented on the consent form) 3) Regularly sexually active and in a mutually monogamous relationship for at least 6 months at study entry 4) Willing to rely on the study IUS as the primary method of contraception during study participation 5) History of regular menstrual cycles defined as occurring every 21-35 days when not using hormones and with a variation of typical cycle length of no more than 5 days 6) Willing to comply with study visit schedule and assessments, including diary completion requirements 7) Planning to reside within a reasonable driving distance of a study research site (approximately 150 miles) for at least 2 years

	Exclusion Criteria Subjects meeting any of the following criteria will be ineligible for study entry: 1) Currently pregnant 2) Pregnant within 4 weeks prior to study entry 3) Planning pregnancy within 24 months of study entry 4) Currently breastfeeding 5) History of ectopic pregnancy without a subsequent intrauterine pregnancy 6) History of trophoblastic disease (benign or malignant gestational) without a subsequent non-trophoblastic intrauterine pregnancy 7) Acute pelvic inflammatory disease or a history of pelvic inflammatory disease without subsequent intrauterine pregnancy 8) History of a positive HIV test or having a partner who is known to be HIV positive 9) History of cervical or vaginal infection (unless successfully treated and considered clinically cured for at least 7 days prior to study entry) 10) Postpartum or post-abortion endometritis unless symptoms resolved at least 4 weeks prior to study entry 11) Current persistent, abnormal vaginal bleeding 12) Abnormal Pap test based on the following criteria: • Pap test in the past 18 months with ASC-US unless: o less than 21 years of age; o a repeat Pap test at least 6 months later was normal; o reflex HPV testing was performed and was negative for high-risk HPV; or o a colposcopy (with or without biopsy) found no evidence of dysplasia requiring treatment or treatment was performed and

	follow-up at least 6 months after the treatment showed no evidence of disease • Pap test in the past 18 months with LSIL unless: o less than 21 years of age; or o a colposcopy (with or without biopsy) found no evidence of dysplasia requiring treatment or treatment was performed and follow-up at least 6 months after the treatment showed no evidence of disease • Pap test in the past 18 months with ASC-H, atypical glandular cells, or HSIL unless colposcopy and/or treatment was performed and follow-up at least 6 months after the colposcopy and/or treatment showed no evidence of disease • Pap test in the past 18 months with malignant cells • Pap test more than 18 months ago that was abnormal without any appropriate follow-up evaluation 13) History of malignancy of the genital tract (e.g. cervical cancer, ovarian cancer, endometrial cancer) 14) History of breast cancer, or suspicion of breast cancer until proven otherwise 15) History of bicornuate uterus or any other abnormality of the uterus resulting in distortion of the uterine cavity or cervical canal incompatible with insertion 16) Known or suspected allergy to levonorgestrel or hypersensitivity to any component of the product 17) Bleeding diathesis (inherited or acquired) 18) Use of anticoagulants within 30 days prior to study entry 19) 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 [Note: any woman

	who may meet this criteria should have a pelvic examination prior to randomization to confirm that the cervix cannot be properly visualized for IUS insertion] 20) Current or history of alcohol, or illicit or prescription drug abuse within 12 months prior to study entry 21) Current use of hormonal contraception for cycle control 22) DMPA (Depo-Provera®/Depo-Ralovera®) injection within the past 9 months (this exclusionary time period can be shortened to 6 months if the subject has also had two spontaneous menstrual cycles [requires minimum of 3 menses] that meet criteria for normal menstrual cycles) 23) Current use of non-contraceptive estrogen, progesterone, testosterone, or other gonadotropins (e.g. hCG) 24) Use of an experimental medication or receipt of an experimental treatment for any condition within 30 days of study entry 25) Study staff or a member of the immediate family of a study staff 26) 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 27) History of 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-IV-TR)
Statistical Methods:	The following analysis populations will be created: • Safety (Safety): All subjects enrolled who underwent the IUS insertion procedure, regardless of age and outcome.

- Modified Intent To Treat (MITT): All LNG20 subjects between 16 and 35 years of age at study entry for whom the assigned IUS is successfully placed in the uterus and for whom there is at least one report of pregnancy status after inserting the IUS.
- Per Protocol (PP): A subset of the MITT population that excludes subjects with major protocol deviations (to be identified prior to data lock).

The Pearl Index with 95% confidence interval for women in the MITT population will be used to establish efficacy for 2 years of use. Cycles (defined as 28 days) during which backup methods of contraception are used will be excluded from the primary analysis of the Pearl Index unless the subject became pregnant in that cycle. Pregnancies judged to have occurred while a study IUS was in place and up to and including 7 days after IUS discontinuation (determined by ultrasound and medical assessment) will be included in these calculations. To establish the efficacy of LNG20 for 2 years of use, acceptable precision of the Pearl Index must be reached during year 1 and, separately, during year 2, where acceptable precision is defined as the upper bound of the 95% confidence interval being no more than 1 unit above the point estimate of the Pearl Index.

Secondarily the Pearl Index will be calculated for use during years 3, 4, 5, 6, 7, 8, 9 and 10.

The Mirena arm of approximately 160 subjects is included as an informative comparator only.

All other secondary endpoint analyses will be descriptive.

Vaginal bleeding patterns (none, spotting, and light, normal, or heavy flow) and dysmenorrhea (none, mild, moderate, or severe) will each be summarized by the percentage of days with a particular pattern during each 90 day intervals after enrollment.

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 by treatment group in addition to changes from baseline. Analysis of a sampling of retained IUSs will be summarized. Levonorgestrel plasma levels will be obtained for all subjects every 6 months and at any IUS discontinuation visit beginning with Month 36 until Protocol Version 9 when thereafter, levonorgestrel plasma levels will be obtained in all subjects at IUS discontinuation and also annually in all women enrolled prior to 31May2011.
Sample Size:	Approximately 1,910 women will be enrolled into the study. Approximately 1,760 women will be assigned to LNG20 or Mirena, with the goal that a minimum of approximately 1,600 LNG20 and 160 Mirena users are enrolled between the ages of 16 and 35 years. Another 150 women 36-45 years of age will be enrolled in a non-randomized cohort and receive LNG20. It is expected that 1,600 LNG20 subjects between the ages of 16 and 35 years will provide at least 10,000 woman-months of exposure in the first two years and at least 360 woman-years of use in the final year of the study for the LNG20.

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ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
ALT	Alanine aminotransferase
ASC-H	Atypical cells cannot exclude high grade changes
ASC-US	Atypical cells of undetermined significance
ASCCP	American Society for Colposcopy and Cervical Pathology
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
BV	Bacterial vaginosis
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
dL	Deciliter
DMPA	Depot Medroxyprogesterone Acetate
EDC	Electronic data capture
EMEA	European Medicines Agency
FDA	Food and Drug Administration
G	Gram
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
HSIL	High grade squamous intraepithelial lesion
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system

IVRS	Interactive voice response system
KOH	Potassium hydroxide
LFT	Liver function test
LNG	Levonorgestrel
LSIL	Low grade squamous intraepithelial lesion
LTFU	Lost to Follow-Up
mcg	Microgram
mg	Milligram
MHRA	Medicines and Healthcare Products Regulatory Agency
MedDRA	Medical Dictionary for Regulatory Activities
mm	Millimeter
PHS	Public health sector
PID	Pelvic inflammatory disease
PK	Pharmacokinetics
SAE	Serious adverse event
SID	Subject identification number
STD	Sexually transmitted disease
WBC	White blood cell
WHO	World Health Organization

1. INTRODUCTION

1.1 Current Intrauterine Contraception Options

1.1.1 History and Clinical Experience to Date

A contraceptive intrauterine device (IUD) is a device inserted into the uterus by a healthcare professional. Most IUDs available today are T-shaped and either contain copper (copper IUD) or deliver a progestin locally to the uterus over a duration of time. A hormone releasing device is most commonly referred to as a contraceptive intrauterine system (IUS). IUDs are highly effective, and the most widely used reversible contraceptive method used by more than 150 million women worldwide (Salem). Based on the latest estimates from 2012, IUDs are used by only 10.3 % of women in the United States practicing contraception with 74% of these IUDs being hormonal (Kavanaugh, 2014). Some barriers to greater use of IUDs in the U.S. include out-of-pocket costs, provider biases, and lack of information (or misinformation) about the safety and effectiveness of current IUDs. Notably, concerns remain that originated from a specific IUD, the Dalkon Shield. Additionally, in a survey of U.S. health care providers, the majority of respondents reported that they had no clinical experience in IUD insertion and removal.

Despite the limited use of IUDs among women in the U.S., almost all users (99%) report being "very satisfied" or "somewhat satisfied" with this method of contraception (ARHP 2004). IUDs are effective immediately after insertion and provide contraceptive benefits for several years. The efficacy of IUDs is equivalent to contraceptive sterilization. The mechanisms of action of IUDs are not fully understood and vary based on type but, through different mechanisms, work primarily to prevent the fertilization of ova by inducing a thickened cervical mucus barrier that sperm are unable to penetrate (Lewis). When IUDs are removed, the return to fertility is rapid. Overall, IUDs are regarded as one of the safest and most clinically cost effective contraceptive methods on the market (Belhadj, Andersson 1992).

Currently there are five IUDs marketed in the United States. A copper-releasing IUD is marketed as ParaGard® T380A by Teva Pharmaceuticals, Inc, three levonorgestrel-releasing intrauterine system (IUS) products marketed by Bayer Healthcare Pharmaceuticals, Inc. under the brand names Mirena®, Skyla® and Kyleena®, and Liletta® (LNG20) by Medicines360.

The ParaGard T380A IUD was approved by the U.S. Food and Drug Administration (FDA) in 1984 and became available for use in 1988. ParaGard is a T-shaped polyethylene device, 32 by 36 mm, containing 380 mm^2 of exposed copper. A monofilament polyethylene white thread is attached to the end of the vertical stem. The copper IUD has a high efficacy rate with 0.7 pregnancies per 100 women in the first year of typical use and is approved for up to 10 years of continuous use. The release of copper ions from the ParaGard IUD is believed to affect sperm motility and viability which impairs fertilization, and to disrupt the normal division of oocytes and the formation of fertilizable ova. Changes also occur in the endometrium that could interfere with the implantation of a fertilized ovum, which explains why this device is particularly effective as a method for emergency contraception.

The Mirena IUS was approved by the U.S. FDA in 2000. The IUS is a T-shaped device, 32 by 32 mm, made of polyethylene. The stem of the device contains a controlled release polydimethylsiloxane membrane surrounding 52 mg of levonorgestrel in a drug reservoir. A monofilament polyethylene brown thread is attached to the end of the vertical stem. Mirena has been studied for safety and efficacy in two large clinical trials in Finland and Sweden (Mirena package insert). In study sites having verifiable data and informed consent, 1169 women 18 to 35 years of age at enrollment used Mirena for up to 5 years, for a total of 45,000 women-months of exposure. The study population was predominantly Caucasian, and over 70% of the participants had previously used IUDs. The reported 12-month pregnancy rates were less than or equal to 0.2 per 100 women and the cumulative 5-year pregnancy rate was approximately 0.7 per 100 women. Mirena is approved for up to 5 years of continuous use for contraception.

The Skyla IUS was approved by the U.S. FDA in 2013. The IUS is a T-shaped device, 28 mm by 30 mm, made of polyethylene. The stem of the device contains a controlled release polydimethylsiloxane membrane surrounding 13.5 mg of levonorgestrel in a drug reservoir. A monofilament polyethylene brown thread is attached to the lower end of the vertical stem. Skyla approval was based on one large clinical trial conducted in eleven countries to determine safety and efficacy (Skyla package insert). In this study, 1,432 women 18 to 35 years of age at enrollment used Skyla for up to 3 years, for a total of 39,368 women-months of exposure. The reported Pearl Index for the first year of use was 0.41. The cumulative 3-year pregnancy rate

was approximately 0.9 per 100 women. Skyla is approved for up to 3 years of continuous use for contraception.

The Kyleena IUS was approved by the U.S. FDA in 2016. The IUS is a T-shaped device, 28 mm by 30 mm, made of polyethylene. The stem of the device contains a controlled release polydimethylsiloxane membrane surrounding 19.5 mg of levonorgestrel in a drug reservoir. A monofilament polyethylene blue thread is attached to the lower end of the vertical stem. Kyleena's approval was based on one large clinical trial conducted in eleven countries to determine safety and efficacy (Kyleena package insert). In this study, 1,452 women 18 to 35 years of age at enrollment used Kyleena for up to 5 years, for a total of 57,313 28-day cycles of exposure. The reported Pearl Index for the first year of use was 0.16. The cumulative 5-year pregnancy rate was approximately 1.45 per 100 women. Kyleena is approved for up to 5 years of continuous use for contraception.

Liletta (LNG20) was initially approved by the U.S. FDA in 2015 for the prevention of pregnancy for up to 3 years of use; in 2017, the U.S. FDA granted approval for up to 4 years of use. Liletta consists of a T-shaped polyethylene frame with a steroid reservoir around the vertical stem. The steroid reservoir is covered with a polydimethylsiloxane membrane that controls the release rate of levonorgestrel from the reservoir. The Liletta reservoir contains 52 mg levonorgestrel, providing an initial release rate of 19.5 mcg/day. The frame is a Nova-T shape and a polypropylene monofilament blue thread is attached to the end of the vertical stem.

In the United States, the current high cost of ParaGard, Mirena, Skyla and Kyleena limits access for low income and underinsured women to these highly effective contraceptive methods. Medicines360 intends to develop a safe, effective and lower cost IUS option for all women requesting long term reversible contraception. The goal of this program is to develop and obtain U.S. regulatory approval for LNG20 and to secure sustainable access for the U.S. public sector at an affordable price.

1.2 Medicines360 Levonorgestrel-Releasing Intrauterine System

The levonorgestrel IUS (LNG20) that Medicines360 has developed 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 LNG20 reservoir contains 52 mg levonorgestrel; providing an initial release rate of approximately 20 mcg/day. A polypropylene monofilament blue thread is attached to the end of the vertical stem. Please refer to the Investigator's Brochure for full details on the components of LNG20.

LNG20 has been investigated in a multi-center, single-blind randomized trial in Europe to assess the therapeutic equivalence in terms of efficacy and safety compared to Mirena in patients with menorrhagia. Enrollment of 280 subjects was completed in January, 2009 and 50% were randomized to LNG20. A review of all safety data supports that LNG20 was generally well tolerated in female subjects with menorrhagia. Serious adverse events (SAEs) collected during the reporting period did not reveal any new safety concerns and did not change the overall risk-benefit evaluation for LNG20. Adverse event-related removals of the IUS occurred in five women (three LNG20, two Mirena). The three LNG20 removals were related to ovarian cysts (one of these three subjects required hospitalization). The two Mirena removals followed development of abdominal and peripheral edema in one subject, and reported nervousness, chest tension, abdominal pain, and hypertension in a second subject. There were 5 SAEs reported in the LNG20 arm. One SAE was assessed as possibly related (Ovarian Cyst) and 3 were assessed as unrelated (Headache, Lumbar Disc Herniation, and Abdominal Colic). An additional unrelated event (Pregnancy) was reported as a SAE because it was an important event. Expulsion rates reported for the first year of use were 4.3% for LNG20 and 3.6% for Mirena.

2. STUDY OBJECTIVES

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

2.1 Primary Objective

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

2.2 Secondary Objectives

The secondary objectives of this study are to assess:

- The safety, tolerability, bleeding patterns, and continuation rates of LNG20
- The occurrence of menses and return to fertility after IUS discontinuation
- The plasma pharmacokinetics of levonorgestrel in a subset of approximately 60 subjects with serial sampling over the duration of use
- Plasma levonorgestrel levels in a subset of 60 subjects (LNG20 arm only) following IUS removal at 121 months of use with sampling at various time points up to 14 days post-IUS removal
- Levonorgestrel plasma levels will be obtained for all subjects at 6 month intervals and at IUS discontinuation visit beginning with Month 36 until Protocol Version 9 when thereafter, levonorgestrel plasma levels will be obtained in all subjects at IUS discontinuation and also annually in all women enrolled prior to 31May2011
- Analysis of an appropriate sampling of IUSs that are removed and, when available, expelled during the study
- The safety and tolerability of LNG20 in a small cohort of women between ages 36 and 45 years
- Endometrial thickness in a subset of 60 subjects at 1, 5 and 10 years of LNG20 use

3. INVESTIGATIONAL PLAN

3.1 Study Design and Plan

This is a Phase 3, randomized, open-label, multicenter evaluation of the efficacy of a levonorgestrel-releasing intrauterine system (LNG20). A marketed levonorgestrel-releasing intrauterine system (Mirena) will be included as an informative comparator.

The goals of the study include provision of information to understand efficacy and safety within the widest range of possible users of the LNG20. Typically, intrauterine contraceptive studies only include women 18-35 years of age for efficacy and safety, and place limits on parity and larger body size. Women outside of these characteristics also desire an effective intrauterine contraceptive. Accordingly, this study will include women who are both nulliparous and parous as well as women

less than 18 years of age in the primary efficacy and safety analyses. Additionally, we will provide safety information on women greater than 35 years of age. Importantly, this study does not restrict enrollment based on weight or BMI as we know that obese and morbidly obese women desire highly effective intrauterine contraception.

Eligible subjects 16-35 years of age will include a minimum of approximately 1,600 subjects using LNG20 and 160 subjects using Mirena. Approximately 650 LNG20 and 160 Mirena subjects were randomized at a 4:1 ratio of LNG20 to Mirena. However, the remaining approximately 950 subjects will be assigned to LNG20 only. Subjects in the Treatment PK substudy (approximately 60), who will be assigned by the IVRS separately from the remainder of study subjects based on BMI. Additionally, approximately 150 eligible females 36-45 years of age will receive LNG20 as part of a non-randomized cohort.

After consent is obtained, screening procedures will be performed and eligible subjects enrolled into the trial via an Interactive Voice Response System (IVRS). Enrollment and IUS insertion may occur on the same day as the screening procedures. The assigned IUS will be inserted by a study Investigator using standardized procedures specific to each system.

The LNG20 16-35 year old enrollment group will be evaluated during study treatment use for up to 121 months, the LNG20 36-45 year old enrollment group for up to 96 months and Mirena subjects for up to 60 months. Study assessments will be performed at a clinic visit at Screening/Enrollment and Months 1, 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114, 120 and 121 (LNG20 36-45 year old enrollment group only through Month 96 and Mirena subjects only through Month 60). Telephone assessments will occur at 3 month intervals between scheduled study visits, starting at Month 9. The IUS will be removed when requested by the subject, when clinically indicated, or at the end of 121 months for the LNG20 16-35 year old enrollment group subjects, 96 months for the LNG20 36-45 year old enrollment group and 60 months of use for Mirena subjects.

All subjects will have a follow-up safety visit one month after discontinuing the study treatment. Additional follow-up will be conducted for subjects who choose a non-hormonal contraceptive method or who indicate that they will attempt to become pregnant, as follows:

- Those women who elect to start a non-hormonal contraceptive method or no contraception (including those desiring pregnancy) will be followed for return of menses

- Those women who desire pregnancy will be followed for up to 12 months to document return to fertility

Pregnancies that occur during study treatment or after IUS discontinuation through the 30-Day Safety Follow-up Visit will be identified through subject query and urine pregnancy testing. A transvaginal ultrasound will be performed for pregnancy dating and to verify if the IUS is still present in the uterus. All pregnancies that occur during treatment (while the IUS is in the subject and up to and including 7 days after IUS discontinuation), will be followed to completion and the outcome recorded.

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

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

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

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

The following substudies will be performed at selected sites:

- Levonorgestrel PK data will be obtained in a subset of approximately 60 subjects (20 non-obese LNG20 subjects, 20 non-obese Mirena subjects and 20 obese LNG20 subjects). In

addition to all procedures outlined in Section 6 for the concomitant primary study visits, LNG plasma samples will be obtained at Enrollment (pre-IUS insertion), Weeks 1 and 2, and Months 1, 3, 6, 9, 12, 18, 24 and 30 after IUS insertion (includes three extra visits at Weeks 1 and 2, and Month 9, not included in the main study). These subjects will be required to give informed consent for participation in the levonorgestrel PK subset (See Section 4.4).

- A subset of 60 subjects assigned to LNG20 and completing 121 months of study treatment will have levonorgestrel samples obtained at various timepoints after IUS removal to characterize the LNG elimination profile. Each subject in this subset will be randomized to one timepoint (one extra visit) post-IUS removal (24 hours, 48 hours, 7 days or 14 days) such that fifteen subjects are randomized to each timepoint.

- A subset of 60 women assigned to LNG20 at selected sites will have transvaginal ultrasound evaluations at enrollment (pre-IUS insertion), 1 year, 5 years and 10 years (pre-IUS removal) to assess changes in endometrial thickness.

3.2 Outcome Measures

3.2.1 Primary Outcome Measure

The primary outcome measure is efficacy of LNG20 at 2 years of use.

This outcome will be established in the MITT population, defined as LNG20 subjects between 16 and 35 years of age with at least one assessment of pregnancy status after successful IUS insertion, by calculating the Pearl Indices for use during year 1 and year 2. The Pearl Index for each year must have acceptable precision, defined as the upper bound of the 95% confidence interval being no more than 1 unit above the point estimate.

3.2.2 Key Secondary Outcome Measures

The key secondary outcome measures are efficacy of LNG20 at 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years and 10 years of use (years 9 and 10 for LNG20 16-35 year enrollment group only).

This outcome will be established in the MITT population by calculating the Pearl Indices for use during year 3, year 4, year 5, year 6, year 7, year 8, year 9 and year 10 (years 9 and 10 for

LNG20 16-35 year enrollment group only). The Pearl Index for each year must have acceptable precision.

3.2.3 Other Secondary Outcome Measures

Other secondary outcomes that will be assessed for LNG20 and Mirena will include:

- Cumulative LNG20 pregnancy rates for years 2 through 10
  - Years 6, 7 and 8 will only include LNG20 subjects
  - Years 9 and 10 will only include the LNG20 16-35 year old enrollment group
- IUS continuation rates at 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years and 10 years
  - Years 6, 7 and 8 will only include LNG20 subjects
  - Years 9 and 10 will only include the LNG20 16-35 year old enrollment group
- IUS expulsion rates at 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years and 10 years
  - Years 6, 7 and 8 will only include LNG20 subjects
  - Years 9 and 10 will only include the LNG20 16-35 year old enrollment group
- IUS safety-related removal rates at 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years and 10 years
  - Years 6, 7 and 8 will only include LNG20 subjects
  - Years 9 and 10 will only include the LNG20 16-35 year old enrollment group
- Vaginal bleeding patterns during IUS use
- Hemoglobin
- Adverse events, including clinically significant laboratory abnormalities
- Pregnancy outcomes will be obtained for all pregnancies that occur while a subject is using the IUS or if the date of conception is up to and including 7 days after IUS discontinuation, including normal births, septic abortions, ectopic pregnancies, birth defects, and premature deliveries, whenever this information can be obtained.
- Fertility rates during the first year following removal of the IUS for those women who desire pregnancy.

- Return to menses. Those women who are using non-hormonal contraceptive methods or no contraception (including those desiring pregnancy) will be followed for up to 3 months for the occurrence of menses following IUS discontinuation. Women who do not menstruate within 3 months following IUS discontinuation will be referred for appropriate evaluation and continue to be followed until menses has occurred or a diagnosis for the cause of the secondary amenorrhea has been established.
- Plasma levonorgestrel levels over the duration of IUS use
- Analysis an appropriate sampling of IUSs that are removed or expelled during the study

Other secondary outcomes that will be assessed for LNG20 will include:

- Plasma levonorgestrel levels over the first 14 days following LNG20 removal after 121 months of use
- Endometrial thickness at 1, 5 and 10 years of LNG20 use as compared to baseline

4. STUDY POPULATION SELECTION

4.1 Subject Selection

Approximately 1,910 subjects will be enrolled in this study, including approximately 1,760 women ages 16 to 35, inclusive, who will be assigned to the LNG20 or Mirena IUS. In addition, a cohort of approximately 150 women between ages 36 and 45 years of age will also be enrolled to receive the LNG20. At least 20% of the subject population is expected to be nulliparous.

4.2 Inclusion Criteria

Study entry (enrollment) is defined as registration of the subject with the IVRS system for IUS assignment. Subjects must fulfill all of the following criteria to be eligible for study entry:

1. Signed informed consent
2. Healthy females 16-45 years old inclusive at the time of enrollment (unemancipated subjects under 18 years old must have written parental consent documented on the consent form)
3. Regularly sexually active and in a mutually monogamous relationship for at least 6 months at study entry

4. Willing to rely on the study IUS as the primary method of contraception during study participation
5. History of regular menstrual cycles defined as occurring every 21-35 days when not using hormones and with a variation of typical cycle length of no more than 5 days
6. Willing to comply with study visit schedule and assessments, including diary completion requirements
7. Planning to reside within a reasonable driving distance of a research site (approximately 150 miles) for at least 2 years

4.3 Exclusion Criteria

Subjects meeting any of the following criteria will be ineligible for study entry:

1. Currently pregnant
2. Pregnant within 4 weeks prior to study entry
3. Planning pregnancy within 24 months of study entry
4. Currently breastfeeding
5. History of ectopic pregnancy without a subsequent intrauterine pregnancy
6. History of trophoblastic disease (benign or malignant gestational) without a subsequent non-trophoblastic intrauterine pregnancy
7. Acute pelvic inflammatory disease or a history of pelvic inflammatory disease without subsequent intrauterine pregnancy
8. History of a positive HIV test or having a partner who is known to be HIV positive
9. History of cervical or vaginal infection (unless successfully treated and considered clinically cured for at least 7 days prior to study entry)
10. Postpartum or post-abortion endometritis unless symptoms resolved at least 4 weeks prior to study entry
11. Current persistent, abnormal vaginal bleeding
12. Abnormal Pap test based on the following criteria:
    - Pap test in the past 18 months with ASC-US unless:
        - less than 21 years of age;

- a repeat Pap test at least 6 months later was normal;
- reflex HPV testing was performed and was negative for high-risk HPV; or
- a colposcopy (with or without biopsy) found no evidence of dysplasia requiring treatment or treatment was performed and follow-up at least 6 months after the treatment showed no evidence of disease;

- Pap test in the past 18 months with LSIL unless:
  - less than 21 years of age;
  - a colposcopy (with or without biopsy) found no evidence of dysplasia requiring treatment or treatment was performed and follow-up at least 6 months after the treatment showed no evidence of disease;
- Pap test in the past 18 months with ASC-H, atypical glandular cells, or HSIL unless colposcopy and/or treatment was performed and follow-up at least 6 months after the colposcopy and/or treatment showed no evidence of disease;
- Pap test in the past 18 months with malignant cells;
- Pap test more than 18 months ago that was abnormal without any appropriate follow-up evaluation

13. History of malignancy of the genital tract (e.g. cervical cancer, ovarian cancer, endometrial cancer)
14. History of breast cancer, or suspicion of breast cancer until proven otherwise
15. History of bicornuate uterus or any other abnormality of the uterus resulting in distortion of the uterine cavity or cervical canal incompatible with insertion
16. Known or suspected allergy to levonorgestrel or hypersensitivity to any component of the product
17. Bleeding diathesis (inherited or acquired)
18. Use of anticoagulants within 30 days prior to study entry
19. 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 [Note: any women who may meet this criteria should have a pelvic

examination prior to enrollment to confirm that the cervix cannot be properly visualized for IUS insertion]

20. Current or history of alcohol or illicit or prescription drug abuse within 12 months prior to study entry
21. Current or prior use of hormonal contraception for cycle control
22. DMPA (Depo-Provera®/Depo-Ralovera®) injection within the past 9 months (this exclusionary time period can be shortened to 6 months if the subject has also had two spontaneous menstrual cycles [requires minimum of 3 menses] that meet criteria for normal menstrual cycles)
23. Current use of non-contraceptive estrogen, progesterone, testosterone or other gonadotropins (e.g. hCG)
24. Use of an experimental medication or receipt of an experimental treatment for any condition within 30 days of study entry
25. Study staff or a member of the immediate family of a study staff
26. 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
27. History of 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-IV-TR)

4.4 Substudies Entry Criteria

4.4.1 Treatment PK Substudy

In addition to meeting all entry criteria for the primary study, subjects desiring to enter the PK substudy must meet all of the following criteria:

- be 16-35 years old at the time of enrollment in the primary study

- have signed informed consent for the PK sampling prior to collection of the blood sample on day of IUS insertion
- have venous access adequate for multiple blood draws
- have not received hormonal contraception within 7 days of enrollment

4.4.2 Endometrial Thickness Substudy

In addition to meeting all entry criteria for the primary study, subjects desiring to enter the substudy assessing endometrial thickness must:

- be 16-35 years old at the time of enrollment in the primary study
- be assigned to LNG20
- have signed informed consent for the endometrial thickness assessments prior to IUS assignment

4.4.3 Elimination PK Substudy

Subjects desiring to enter the elimination PK substudy must meet all of the following criteria:

- be 16-35 years old at the time of enrollment in the primary study
- have been assigned to LNG20
- have completed 121 months of LNG20 use
- have signed informed consent for the elimination PK sampling prior to randomization for the elimination PK sampling timepoint
- not use hormonal contraception and not attempt to become pregnant during substudy participation such that the subject agrees to one or more of the following criteria:
    - sexually abstinent for up to 2 weeks
    - use of a non-hormonal method of birth control for up to 2 weeks

5. STUDY TREATMENTS

After written consent has been obtained and eligibility has been established, the subject will be assigned a subject identification number and assigned by IVRS to either LNG20 or Mirena (except those 36 to 45 years old who will only receive LNG20). The LNG20 IUS may be used for up to 121 continuous months for the LNG20 16-35 year old enrollment group, 96 continuous months for the LNG20 36-45 year old enrollment group and the Mirena IUS may be used for up to 60

continuous months. Only the assigned IUS may be inserted into the respective subject.

5.1 LNG20 IUS (Dosage and Formulation)

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

5.2 Mirena IUS (Dosage and Formulation)

This T-shaped polyethylene device contains 52 mg of levonorgestrel. For further details, see the Mirena Package Insert in the Study Reference Manual.

5.3 IUS Supply and Administration

Each IUS is packaged as a single use sterile system. Accessories that are used for IUS insertion into the uterine cavity and do not remain in permanent contact with the subject are included in the sterile package with the IUS. The IUS with the accessories should be stored in its sterile sealed package until insertion.

See the Investigator's Brochure for LNG20 product description, the Study Reference Manual for Mirena product description, and the Study Reference Manual for LNG20 and Mirena insertion and removal instructions.

5.4 IUS Storage and Accountability

LNG20 and Mirena 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. 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 and collected for analysis. Storage and shipping procedures to return removed and expelled IUSs are detailed in the Study Reference Manual.

For unsuccessful insertions all IUSs and their associated inserters will be stored at the site for potential analysis. The sponsor will notify the site which IUSs with their associated inserters will require to be shipped or may be destroyed on site. Storage and shipping procedures for unsuccessful insertion IUSs and inserters are detailed in the Study Reference Manual.

5.5 IUS Replacement

No IUSs will be replaced if an expulsion or removal occurs. No subjects will be eligible for temporary IUS removal.

5.6 Concomitant and Excluded Therapy

Concomitant medications are any prescription medications or over-the-counter preparations used by the subject between 7 days prior to enrollment (30 days for anticoagulants) and 30 days following IUS discontinuation. All concomitant medications, including excluded therapies, must be documented in the Concomitant Medication CRF. Subjects who begin to chronically 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 with the following exceptions:
    - An oral, transdermal, vaginal or combined monthly injectable hormonal contraceptive may be used in the first month only as outlined in Section 6.3;
    - Emergency contraception should be recommended in any situation when the subject feels the IUS expelled and she subsequently had intercourse. Subjects will not be discontinued from the study because of emergency contraceptive use.
- A previously inserted contraceptive implant, IUD or IUS unless the implant, IUD or IUS is removed prior to study IUS insertion (may be removed immediately before study IUS insertion).
- Any other contraceptive method that could obscure the efficacy parameters of this investigational contraceptive should not be used during study participation. However, if the subject feels the need to protect herself against sexually transmitted infections, she should be advised to use a male condom. If the use of a male condom becomes a regular part of the subject's contraception, the site Principal Investigator should check with the Medical Monitor

about possibly discontinuing the subject from study participation. All condom usage will be documented on the daily subject diaries.

- Any non-contraceptive estrogen, progesterone, testosterone, or gonadotropin (e.g. hCG)
- Misoprostol on day before or day of IUS insertion or removal
- Any cervical dilating instrument used during IUS insertion other than Pratt dilators, a lacrimal duct probe or an os finder
- Any investigational treatment or medication other than the LNG20.

5.7 Blinding

This is an unblinded, open-label study.

6. STUDY PROCEDURES

A flowchart of study assessments is in Appendix A.

6.1 Clinical Laboratory Tests

The site's local laboratory will be used for hematology, chemistry, quantitative hCG, Chlamydia, gonorrhea, and Pap test evaluations. High sensitivity urine pregnancy testing may be performed in the clinic. Plasma levonorgestrel samples will be obtained, processed, packaged and shipped to the central clinical lab per the instructions provided in the Laboratory Operations Manual. HIV and any other clinically appropriate STD testing are recommended per CDC guidelines for any subject with a change in sexual partner since her last examination; subjects should be referred for such testing within the local standard of care.

6.2 IUS Insertion Definitions

- An **insertion attempt** is considered to start with the assignment of the IUS in the IVRS and the opening of the LNG20 kit with the intent to perform an insertion, unless there was a notable product defect upon inspection of the product
- The **insertion procedure** is considered to have started once the speculum is placed for the purpose of IUS insertion. No instrumentation of the cervix can occur prior to contacting the

IVRS during the enrollment visit. The insertion procedure is considered to have ended with the removal of the speculum

- **IUS insertion** starts with placement of any instrument, device or needle into or on the cervix. IUS insertion ends with completion of cutting the IUS threads following successful intrauterine IUS placement
- **IUS insertion failure** is considered to occur when after contact with the external cervical os with the inserter the completion of IUS insertion is not achieved. Loss of product sterility due to clinician error is also considered a failed insertion
- **Successful IUS insertion** is considered as retention of the IUS in the uterus through the cutting of the strings; the day of successful IUS insertion is considered Study Day 1

6.3 Screening/Enrollment Visit

Screening is considered to start with the signing of the Informed Consent Form by the subject. Although the Screening and Enrollment Visits may occur during one visit, the Screening procedures may be performed over multiple days. The Enrollment Visit is considered to be on the date the subject is assigned through the IVRS. Screening test results are not required to be available prior to the Enrollment Visit.

Scheduling of the Enrollment Visit must take the following schemes into account:

- When switching from an oral, transdermal or vaginal hormonal contraceptive, the subject should continue that method after the study IUS insertion until the end of the current cycle. If using the contraceptive continuously (without a hormone free interval), then discontinue 7 days after IUS insertion. When possible, the Enrollment Visit should be scheduled during the hormone-free time of the cycle (i.e., "placebo week," "patch-free week," or "ring-free week")
- When switching from an injectable monthly combined hormonal injection, the study IUS insertion may occur anytime within 28 days of the last injection
- When switching from non-hormonal contraception (except copper IUD), the study IUS insertion **must** be performed within the first 7 days of the menstrual cycle

- When switching from a contraceptive implant, another hormonal IUS, or a copper IUD, the study IUS insertion may occur anytime in the menstrual cycle but should occur on the same day as removal of the implant, non-study IUS, or IUD
- Women who need a screening Pap test (see section 6.11) should be scheduled for screening on a day they are expected to have minimal or no bleeding
- All enrollment procedures must be completed within 30 days of screening. If greater than thirty days, Medical Monitor approval must be obtained before rescreening or enrollment

6.3.1 Screening Procedures

All screening procedures must be performed before Enrollment Visit procedures. Although screening test results are not required to be available prior to the Enrollment Visit, all specimens for screening laboratory testing must be collected prior to enrollment (IVRS contact).

- Written informed consent prior to conducting any study specific procedures
- Demographic information
- Medical history, including pregnancy, contraception, menstrual cycles, and vaginal bleeding and cramping patterns
- Medication history for 7 days prior to enrollment (anticoagulant use for 30 days)
- High sensitivity urine pregnancy test (positive test would exclude subject)
- Height, weight, temperature, and blood pressure (all must be measured at the Screening Visit)
- Breast exam and any clinically indicated physical examination
- Pelvic exam, STD testing and Pap test:
    - Pelvic exam, STD testing and Pap test (if not required for eligibility) may be deferred to the time of IUS insertion if screening and enrollment visits occur on the same day and there is otherwise no clinical reason to perform the pelvic examination prior to enrollment
    - Pap test for eligibility:
        - All subjects over 20 years and 6 months old require a Pap test for eligibility from within the last 18 months (see section 6.11)

        - Enrollment and IUS insertion may not occur until eligibility with a documented test is confirmed
    - Chlamydia testing for all subjects
    - Gonorrhea testing for any subject following a change in sexual partner since last tested or if never tested after change. In addition, HIV and other related sexually transmitted infection testing is recommended
- Hemoglobin, Serum creatinine, AST, ALT, and bilirubin
- Review eligibility criteria (subject failing to meet all inclusion/exclusion criteria are to be recorded as Screen Failures)

6.3.2 Enrollment Visit Procedures

Once the IVRS is contacted and an IUS is assigned, the subject is considered enrolled. Insertion of the assigned IUS must be attempted on the same day the IVRS assignment occurs. Second insertion attempts are allowed and can occur on a different day, but must be within 30 days of signing the informed consent. The day of successful IUS insertion is considered Study Day 1. Enrollment procedures and study IUS insertion must be scheduled per the guidelines outlined in Section 6.3. If screening and enrollment are occurring on the same day, all screening laboratory blood or urine testing must be collected prior to enrollment in the IVRS; cervical tests may be collected at the time of insertion.

- For women having enrollment on the same day as screening:
    - Perform all screening procedures prior to contacting the IVRS except for the pelvic exam and any cervical testing which can be performed as a continuum with the insertion procedure *EXCEPTION*: a separate pelvic exam must be completed prior to contacting the IVRS if there is clinical suspicion that anatomical issues may prevent successful insertion
- For women having enrollment on a different day than screening, include the following:
    - Repeat a high sensitivity urine pregnancy test prior to calling the IVRS
    - Review results of screening tests, if available:
        - If screening test results **are not** available prior to enrollment

- Enrollment may proceed **unless** an entry criteria Pap test result is pending (See section 6.11)

- If screening test results **are** available prior to enrollment:
  - If a Pap test was performed and meets the exclusion criteria, the subject must not be enrolled; however, she can be re-screened if entry criteria are satisfied at a future date
  - If STD testing (Chlamydia or gonorrhea) is positive, enrollment must be delayed until the subject completes appropriate antibiotic treatment
  - If tests are appropriately collected but reported unevaluable prior to enrollment or successful insertion the tests must be repeated

- Enrollment procedures:
  - Confirm eligibility criteria
  - Enroll in IVRS
  - Insert IVRS assigned study IUS using the techniques described in the Investigator's Brochure.
    - Up to two attempts for insertion can be made. Each attempt should use a new IUS of the assigned treatment group. The IVRS must be contacted before each attempt
    - 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
  - Dispense diaries and instruct subjects on diary completion (see Study Reference Manual)

- 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.
  - Call for an urgent study visit if she:
    - Suspects she is pregnant
    - Has expelled the IUS (If IUS is retained, it should be provided to the to the study site at the visit which will be an Early Discontinuation Visit.). Subject should be instructed not to rinse the expelled IUS
    - Has symptoms of a pelvic infection
    - Does not feel the strings
    - 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 HIV and STD precautions
- Schedule next appointment

6.4 Post-Insertion Study Follow-Up Visits

Post-insertion study follow-up evaluations will occur at Months 1, 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114 and 120 (LNG20 36-45 year old group only through Month 90 and Mirena subjects only through Month 54). The visits should occur within 14 days before or after the expected calendar visit date (within 7 days for the Month 1 and 3 visits).

- Diaries
  - Collect diaries and review for appropriate completion.
    - Confirm menstrual bleeding and cramping information is entered correctly (Months 1, 3, 6, 12, 18, and 24 only)
    - Confirm other contraception use is entered correctly

- Confirm compliance with study IUS by reviewing other contraception method(s) documented in diaries.
- The IUS would be considered her primary method of contraception if no regular use of other contraception is indicted on the diaries

  - Dispense additional diaries as needed

- Medical review
  - Review of adverse events or changes in medical history
  - Review of concomitant medications
  - Complete Bleeding/Cramping Form
    - All subjects: Months 30, 36, 42, 48 and 54
    - All LNG20 subjects: also Months 60, 66, 72, 78, 84
    - LNG20 16-35 year old enrollment group: also Months 90, 96, 102, 108, 114 and 120
  - Inquire about change in sexual partner
- Collection of blood sample for
  - Hemoglobin
    - All subjects: Month 12
    - All LNG20 subjects: also Month 60
    - LNG20 16-35 year old enrollment group only: Also Month 120
  - Plasma levonorgestrel
    - All subjects: Months 36, 42, 48 and 54
    - LNG20 subjects enrolled prior to 31May2011:
      - LNG20 16-35 year old enrollment group: also Months 60, 72, 84, 96, 108 and 120
      - LNG20 36-45 year old enrollment group: also Months 60, 72 and 84
- Physical examination and testing
  - High sensitivity urine pregnancy test (if positive, see Sections 7.4 and 7.5)
  - Weight and blood pressure (both must be measured at each visit)
  - Breast exam
    - All subjects: Months 12, 24, 36 and 48
    - All LNG20 subjects: also Months 60, 72 and 84

        - LNG20 16-35 year old enrollment group: also Months 96, 108 and 120
    - Any clinically indicated physical examination
    - Clinically verify presence of IUS by palpation or direct visualization of strings (for missing strings management see Section 6.14 and Appendix C
    - Pelvic exam
        - All subjects: Months 12, 24, 36 and 48
        - All LNG20 subjects: also Months 60, 72, 84
        - LNG20 16-35 year old enrollment group: also Months 96, 108 and 120
    - Pap test if indicated, see section 6.11
        - All subjects: Months 12, 24, 36 and 48
        - All LNG20 subjects: also Months 60, 72, 84
        - LNG20 16-35 year old enrollment group: also Months 96, 108 and 120
    - STD testing:
        - Chlamydia testing for all subjects 25 years old or younger
            - All subjects: Months 12, 24, 36 and 48
            - All LNG20 subjects: also Months 60, 72, 84
            - LNG20 16-35 year old enrollment group: also Months 96, 108 and 120
        - Chlamydia and gonorrhea testing for any subject following a change in sexual partner since the last study visit. In addition HIV and any other appropriate STD testing should be performed as recommended by the CDC.
- Interview subject regarding future plans for relocation or discontinuation
- Month 90 visit for LNG20 36-45 year old enrollment group and Month 120 visit for LNG20 16-35 year old enrollment group: Discuss contraception options in preparation for the upcoming Discontinuation Visit such that the subject can immediately initiate another method (the site should attempt to have her desired method available) or be abstinent to:
    - Avoid conception within 7 days after IUS discontinuation
    - Enable the subject to avoid undesired pregnancy
- Schedule next appointment

6.5 Contacts Between Study Visits

Telephone or e-mail contacts for safety evaluation will occur at the end of 9, 15, 21, 27, 33, 39, 45, 51, 57, 63, 69, 75, 81, 87, 93, 99, 105, 111 and 117 months of use (LNG20 36-45 year old enrollment group only through Month 93 and Mirena subjects only through Month 57). The contacts should occur within 14 days before or after the expected contact date.

- Review of adverse events or changes in medical history
- Review of concomitant medications
- Review contraception method history since last scheduled study contact. The IUS would be considered to be her primary method of contraception if no regular use of other contraception is indicated on the diaries.
- Complete Bleeding/Cramping Form
    - All subjects: Months 27, 33, 39, 45, 51 and 57
    - All LNG20 subjects: also Months 63, 69, 75, 81, 87, 93
    - LNG20 16-35 year old enrollment group: also Months 99, 105, 111 and 117
- Inquire about change in sexual partner. If a contact elicits that there has been a change in sexual partner since the last time the subject had STD testing, she should be asked to come to the office for an Unscheduled Visit for Chlamydia and gonorrhea testing. In addition, HIV and any other appropriate STD testing should be performed as per CDC recommendations.
- Interview subject regarding future plans for relocation or discontinuation
- LNG20 subjects who are beyond the Month 90 study visit at the time that an investigative site obtains Institutional Review Board approval of Protocol Version 9.0 will be informed about the amendment changes at the Month 93 telephone contact or, if the Month 93 telephone contact has already occurred, at an additional telephone contact.

- Telephone contact prior to any early IUS discontinuation:
    - Discuss contraception options in preparation for the upcoming Discontinuation Visit such that the subject can immediately initiate another method (the site should attempt to have her desired method available) or be abstinent to:
        - Avoid conception within 7 days after IUS discontinuation
        - Enable the subject to avoid undesired pregnancy
    - Request the subject not have intercourse for at least 24 hours before the Discontinuation Visit; the visit may need to be rescheduled if the subject has intercourse within 24 hours of IUS removal
- Confirmation of next scheduled appointment

6.6 Study Treatment Completion/Early Discontinuation

Study treatment completion will occur at the end of 60 months of Mirena IUS use, 96 months of LNG20 IUS use for the 36-45 year old enrollment group or 121 months of LNG20 IUS use in the 16-35 year old enrollment group. The visit should occur within 14 days before or after the completion of 60 months of Mirena use or 96 months for the LNG20 IUS 36-45 year old enrollment group; the visit should occur within 7 days before or after the completion of 121 months of use for the LNG20 IUS 16-35 year old enrollment group. The same assessments should be performed if Early Discontinuation occurs.

- Inquire about last intercourse; if possible, any subjects who had intercourse (with intravaginal ejaculation) within the preceding 24 hours should have the Discontinuation Visit rescheduled to a time more than 24 hours from intercourse.
- Collect diaries and review for appropriate completion. Confirm compliance with study IUS by reviewing contraception method(s) documented in diaries since the last scheduled study contact.
- Complete Bleeding/Cramping Form (**only** if discontinuation after Month 24)
    - Include only information since the last time the form was completed;
    - If the last study visit or contact (phone or email) was more than 3 months ago, only include the information for last 3 months;

  - If Early Discontinuation is during Months 25- 27, include only information beginning with Month 25
- Review of adverse events or changes in medical history
- Review of concomitant medications
- Inquire about change in sexual partner
- Collection of blood sample for:
  - Hemoglobin if not done within the last 3 months
  - Plasma levonorgestrel (only if after Month 36 or for subjects participating in the PK Substudy) if not done within the last 3 months
- High sensitivity urine pregnancy test (if positive, see Sections 7.4 and 7.5)
- Weight and blood pressure
- Breast and pelvic exam (if not performed within the last 3 months)
- Any clinically indicated physical examination
- Pap test if indicated, see section 6.11
- STD testing:
  - Chlamydia testing for all subjects 25 years old or younger who have not had any testing within the last 6 months
  - Chlamydia and gonorrhea testing for any subject following a change in sexual partner since the last study visit. In addition HIV and any other appropriate STD testing should be performed as recommended by the CDC
- Removal of IUS, if not already expelled or removed (at an outside location)
- Retain all removed or expelled IUSs (when possible) per the Study Reference Manual
- Contraceptive counseling
  - Immediate initiation of another method in the office when possible
  - Request to use this method or be abstinent for at least one week to avoid conception within 7 days after IUS discontinuation
- Schedule next appointment

6.7 30-Day Safety Follow-Up

All subjects must have a safety follow-up visit between 30 and 43 days after the Treatment

Completion/Early Discontinuation Visit (except those made lost to follow up or who withdrew consent per section 7.18). If the subject contacts the office with an expulsion that was 30 or more days ago, this visit may be combined with the Early Discontinuation visit.

- Review of adverse events (note: all adverse events occurring within 30 days of IUS discontinuation should be reported on the appropriate adverse event CRF)
- Review of concomitant medications used up to 30 days of IUS discontinuation
- Menstrual history if not using a hormonal method of contraception
- High sensitivity urine pregnancy test (if positive, see Sections 7.4 and 7.5)
- Weight and blood pressure
- Additional contraceptive counseling if needed
- Review with subject that continued telephone or clinic follow-up (as appropriate) is indicated for the following:
    - an ongoing IUS-related adverse event at study discontinuation should be followed monthly until the adverse event resolves or has stabilized
    - any subject electing to use a non-hormonal contraceptive method or no contraception (including those desiring pregnancy) will be followed monthly for up to 3 months after IUS removal/expulsion for return of menses. Any woman who does not menstruate within 3 months following IUS discontinuation will be referred for appropriate evaluation and continue to be followed monthly until menses has occurred or a diagnosis for the cause of the secondary amenorrhea has been established
- Those women desiring a pregnancy after IUS discontinuation will be contacted every three months from their Treatment Completion/Early Discontinuation Visit up to one year to record return to fertility.
    - Once a pregnancy is reported no further follow-up contact is required.
    - Women who do not become pregnant and change their intention before completing a full 12 months of follow-up will be discontinued from the study and not be included in the return to fertility cohort.

6.8 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 safety, the IUS or study participation, 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.

6.9 Diagnostic Ultrasound Examinations

Diagnostic ultrasound examinations may be required during the study to evaluate pregnancy (see Appendix B), missing IUS strings (see Appendix C), 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. A 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.

6.10 Substudy Procedures

6.10.1 Treatment PK Substudy

Subjects in this substudy will consist of two cohorts based on BMI. Forty non-obese (BMI <30 kg/m^2) women will be randomized by the IVRS separately from the main study subjects in a 1:1 ratio to LNG20 or Mirena. In addition, twenty obese (BMI≥30 kg/m^2) women will receive the LNG20. Blood samples will be collected for plasma levonorgestrel levels at the Enrollment Visit before insertion of the IUS, and then at Days 7 and 14, and Months 1, 3, 6, 9, 12 18, 24, 30 and at

Early Discontinuation. A window of plus or minus 1 day is allowed for the Week 1 and 2 visits, and a window of plus or minus 3 days is allowed for the subsequent month visits to allow for scheduling. The PK sampling will require three extra study visits for blood draws only on Days 7 and 14 (no other study procedures are required at those visits), and for blood draw and Month 9 Contact procedures. All other PK sampling visits should be performed in conjunction with the corresponding primary study visits. For details regarding PK blood sample collecting, processing and shipping, see the PK Lab Manual.

6.10.2 Endometrial Thickness Substudy

Subjects in this substudy will be assigned the LNG20. Endometrial thickness assessments will be made at Enrollment (pre-IUS insertion), Month 12, Month 60 and Month 120 study visits. The assessment at Enrollment should occur after IVRS assignment to LNG20 and before IUS insertion. If IUS removal is planned at the same study visit, the endometrial thickness assessment should occur before IUS removal. Endometrial thickness should not be assessed at any other visits, including an early Discontinuation Visit (unless that visit is occurring at Month 12, Month 60 or Month 120). Endometrial thickness is defined as the maximal dimension of the endometrial cavity in the anterior-posterior plane of the uterus, including all contents of the endometrial cavity, and will be measured in a longitudinal view of the uterine cavity using transvaginal sonography.

6.10.3 Elimination PK Substudy

Subjects in this substudy will consist of those who are assigned the LNG20, have completed 121 months of IUS use, signed appropriate consent to participate in the substudy and meet the contraceptive requirements (see Section 4.4.3). Each subject will be randomized to one time point post-IUS removal at either 24 hours, 48 hours, 7 days or 14 days. There is a window of plus or minus 2 hours for the PK sampling of 24 hours and 48 hours, and a window of plus or minus 1 day for the 7 day and 14 day blood sample collection. The PK sampling day will be one extra study visit for the blood draw only and no other study procedures are required at that visit. The subject's participation in the substudy is considered complete once the PK sample is collected.

6.11 Pap Testing

Pap test criteria for study entry are outlined in Section 4.3.

General concepts:

- Eligibility Pap testing at screening must be performed in all women 20 years 6 months of age or older if no documented Pap test has been performed in the last 18 months. The enrollment visit cannot be performed until this Pap test result is available and the subject meets entry criteria
- Based on her age, if a subject will be due for a Pap test within 6 months on either side of the screening or annual study visit, a Pap test should be performed at that visit
- A copy of any Pap test or follow-up testing used for determination of study eligibility or during study follow-up must be obtained and included in the study record. If not available at the time of the visit for which the documentation is required then the Pap test should be performed per protocol
- For routine follow-up Pap testing, a Pap test obtained at an outside location within 6 months prior to the scheduled study visit can be used in place of the study Pap test as long as a written copy of results is obtained
- Pap testing is not required for Early Discontinuation if a Pap test has been done within the last 18 months and is otherwise not clinically indicated
- An abnormal Pap test that was treated before the study should still have follow-up as per the ASCCP guidelines (it is a pre-existing condition that still needs appropriate follow-up)

Pap testing at screening and study follow-up is indicated as follows:

- Women <20 years and 6 months of age: no Pap test is required at screening or any follow-up examination. Once the subject is 20 years 6 months of age, Pap testing should be performed at screening and/or "annual" visits (Months 12, 24, 36, 48, 60, 72, 84, 96, 102, 108, 114 and 120, as applicable)
- Women ≥ 20 years and 6 months:
  - Screening
    - If the subject has a normal Pap test within the last 18 months then Pap testing does not need to performed at the screening visit
    - If the subject has not had a Pap test in the past 18 months or does not have a written copy of a normal Pap test, then a Pap test should be performed at the screening visit

- If the subject has had an abnormal Pap test within the last 18 months but meets study entry criteria regarding abnormal Pap tests then one should be performed at the screening visit only if indicated as part of the routine follow-up of the abnormal Pap test (see Section 6.12)

- Follow-up Pap tests
  - For women who are currently immunosuppressed or HIV positive, Pap testing should be performed annually as long as the Pap tests remain normal (for abnormal Pap test follow-up, see section 6.12)
  - For women who have a history of treated CIN II or CIN III, Pap and HPV testing should be performed (or have been performed) at 12, 24 and 60 months after treatment as long as the Pap and HPV tests remain normal (for abnormal Pap test follow-up, see section 6.12); those women who had normal testing and are more than 60 months from treatment can undergo routine screening
  - All other women should have follow-up Pap testing every 3 years at the "annual" visit (Months 12, 24, 36, 48, 60, 72, 84, 96, 108 and 120, as applicable) as long as the Pap tests remain normal (for abnormal Pap test follow-up, see section 6.12)

High-risk (HR) HPV testing: HR HPV testing is not required but if performed as part of routine off-protocol testing then:

- Prior HR HPV tests or tests obtained during the study as part of routine screening for women ≥30 years will not be used to alter the timing of Pap testing.
- Reflex HR HPV testing for triage of ASCUS Pap tests in women more than 24 years of age can be used to discern if a Pap is considered normal (ASCUS/HR HPV negative) or abnormal (ASCUS/HR HPV positive)

6.12 Management of Abnormal Testing During the Study

- Any clinically significant abnormalities of the screening procedures that are exclusionary but reported after successful IUS insertion will be recorded as pre-treatment medical history and not as a protocol violation
- Clinically significant study-related results should be managed as follows:
  - Vaginal wet prep/KOH prep: treatment in accordance with current CDC guidelines for trichomoniasis, symptomatic BV, and symptomatic yeast infection

- Pap test: refer for colposcopy and treatment (if indicated) as per local or ASCCP guidelines (www.asccp.org). The study IUS should not be removed because of an abnormal Pap test or need for colposcopy or treatment
- Gonorrhea or Chlamydia: treatment in accordance with current CDC guidelines. The IUS should not be removed because of a positive test or a diagnosis of cervicitis
- Hemoglobin: a value consistent with anemia should be evaluated and treated within the local standard of care

  Serum creatinine, AST, ALT, and bilirubin: any clinically significant abnormalities of the screening labs should result in appropriate evaluation/referral and be recorded as past medical history

6.13 Management of Unevaluable Testing During the Study

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

- Screening Visit Tests
  - If appropriately collected prior to enrollment and results reported after successful IUS insertion, it is not a protocol deviation
  - Repeat testing should occur as follows:
    - If screening and enrollment are not scheduled on the same day, the unevaluable tests should be repeated ***prior*** to enrollment
    - If screening and enrollment occurred on the same day, or successful insertion occurred prior to obtaining the test results, the unevaluable tests should be repeated as follows:
      - hemoglobin, serum creatinine, AST, ALT, or bilirubin: next study visit (second IUS insertion attempt, or Month 1 as applicable)
      - Chlamydia and/or gonorrhea: as soon as possible (as an Unscheduled Visit or at the next scheduled visit, if an unscheduled visit is not possible)
- Non-Screening Visit Tests
  - Pap test: repeat at next study visit
  - Chlamydia and/or gonorrhea, hemoglobin, or quantitative hCG: repeat as soon as possible (as an Unscheduled Visit)

7. RISK-BENEFIT AND SAFETY ASSESSMENTS

7.1 Risks

7.1.1 Contraceptive Failure

Overall

There is always a potential risk that a method of contraception may not prevent pregnancy. The Mirena package labeling lists its contraceptive failure as a 12-month pregnancy rate less than or equal to 0.2 per 100 women and a 5-year rate of approximately 0.7 per 100 women.

A five-year multicenter trial enrolled 1,821 women to receive a Mirena and 937 women to receive a copper IUD (Nova T) with 200 mm^2 of copper on the stem (Andersson 1994). During the 60 month observation period, 5 (0.5%) women became pregnant with the Mirena and 35 (5.9%) with the Nova T ($p<0.001$). Of the five pregnancies in the Mirena group, two occurred after unrecognized expulsions. One pregnancy occurred in the first year, one in the second year, one in the third year and two in the fourth year of use.

A Finnish survey study gathered data from 17,360 women in 1996 using the Mirena (Backman). The total exposure was 58,600 woman-years. Of the 132 pregnancies reported, hospital records could be obtained for 108 cases. Of the reviewed cases, only 40 cases occurred with the Mirena *in situ*. For the other 68 women, only 7 had an unrecognized expulsion. The other women either became pregnant after removal, before insertion, or were not really pregnant. If the 24 unconfirmed cases are counted as true Mirena failures, then 71 of these 17,360 women had a failure. The one and five-year pregnancy rates are approximately 0.1 and 0.5 per 100 women, respectively, and the Pearl Indices were 0.1 and 0.11, respectively.

Clinical data is available to support use of the 52 mg LNG-releasing IUS beyond 5 years (Wu and Pickle). A randomized controlled trial comparing Mirena and a TCu380A IUD evaluated the efficacy of both products through 7 years of use (Rowe, 2016). A total of 3,836 women were enrolled at 20 centers in Europe, Asia, South America, and China and were randomly assigned to one of the 2 products. Eligible women were 16 to 40 years old, parous, and without known leiomyoma or recent pelvic infection. After excluding 15 failed insertions, 1,910 women received Mirena and 1,911 received a TCu380A. Ultimately, 398 women in the Mirena group

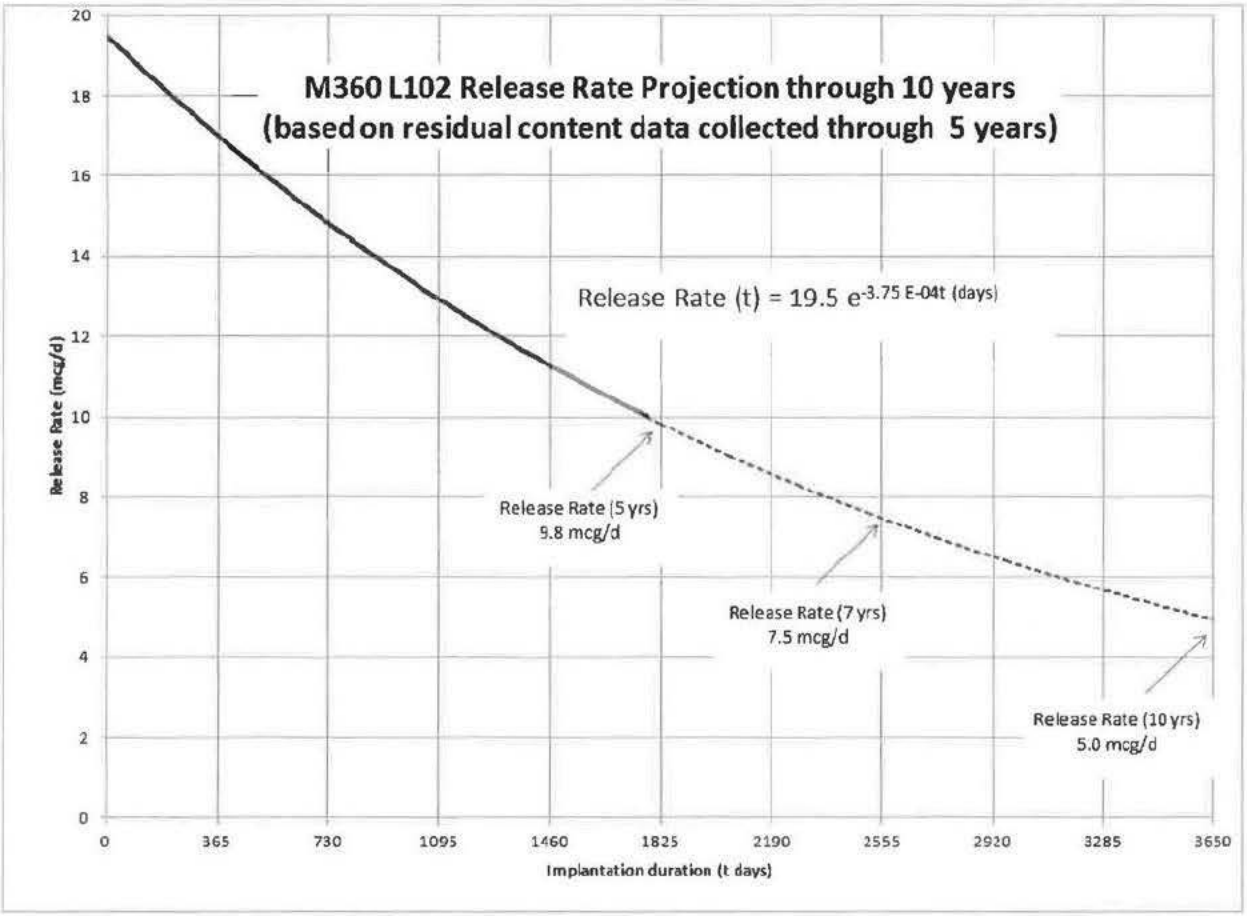
and 682 in the TCu380A group completed 7-year follow-up with the product in place. The cumulative 7-year pregnancy rate among Mirena users was significantly lower than among TCu380A users (0.53 per 100 women vs 2.45 per 100 women, respectively). All pregnancies in the Mirena group occurred in the first 5 years of study follow-up—with no pregnancies in years 6 through 7. Additionally, two small observational trials have been reported that included women enrolled in sponsor-funded studies that chose to continue the product beyond 5 years. The first study, from a single center in Sweden, included 109 multiparous women who extended use for 5.3 to 8.0 years (Rönnerdag and Odlind, 1999). There are no clear data on the number of women who reached specific time points beyond 5 years of use. The other study included 87 parous women with a mean age of 33 years at the time the LNG IUS had been used for 5 years who were followed through 84 months of exposure (467 woman-years of observation from years 5 to 7) (Hidalgo et al., 2009). No pregnancies were observed in either study.

Rönnerdag et al (1999) evaluated 82 women entering year 8 of Mirena use who planned to continue use for up to 4 years (year 12), although the maximum duration of continuous use was 13.3 years. At the end of follow-up, the mean age was 44.7 years (range 33.5-51.5 years). No pregnancies occurred during years 8 to 12. Of the 82 women, 4 were lost to follow-up. Five others terminated IUS use including one who desired pregnancy, one partial expulsion, one suspected PID 3 years after placement and two for personal reasons.

Heikinheimo et al (2014) evaluated approximately 160 women entering year 8 of Mirena use and 144 completed 10 years of use. The authors reported the mean age of the population after the first 6 continuous years of use, which was 38.7 ± 4.5 years and 59% were less than 40 years at that time. The exact reasons for discontinuations during years 8 to 10 are not described. No pregnancies occurred during years 8 to 10.

Additional data to support extension to 10 years of continuous use is available from *ex vivo* release rates for the LNG20 IUS as compared to known data for the recently approved Skyla LNG-releasing IUS with contraceptive efficacy recognized by the CDC as highly effective. The initial LNG release rate for Skyla is 14 mcg/day and decreases to 5 mcg/day after 3 years, averaging 6 mcg/day over 3 years (Skyla package insert). The levonorgestrel release rate at the end of 10 years of use of the LNG20 IUS is projected to be 5.0 mcg/day based on extrapolation

of the average release rates calculated from LNG20 residual content data collected under this protocol over the first 5.4 years of use.



When pregnancy continues with Mirena or the LNG20 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). 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). It is unknown whether these risks are similar for women who conceive while using a LNG IUS.

If pregnancy occurs during study treatment, the subject will be instructed that the LNG 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 B.

The occurrence of pregnancies will be monitored on an ongoing basis. Unacceptably high rates of accidental pregnancies will be reviewed by the IDMC for decisions regarding study continuation. 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.

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 that occurred with the LNG IUS *in situ*, 8 (53%, 95% CI 28, 79%) ended in miscarriage. Of the 5 pregnancies reported by Andersson 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.

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. The rate of ectopic pregnancy with Mirena use is approximately .02 to .06 per 100 women years (Andersson 1994, Backman). Of women who become pregnant while using a LNG IUS, as many as one-half will have an ectopic pregnancy (Backman). In all, ectopic pregnancy is very rare but cannot be completely excluded with the use of Mirena or LNG20.

7.1.2 Difficult Insertion/Removal

In a study of 224 nulliparous women receiving the LNG-IUS, only 6 (2.7%) insertions were unsuccessful (Marions). The insertions, mostly carried out by midwives, were regarded as easy by 72% of the inserters. Nineteen (9%) women considered the procedure to have been painless, 162 (72%) moderately painful, and 39 (17%), severely painful.

Jensen et al. reported a series of 509 parous US women who received Mirena in a clinical trial. Successful insertions were accomplished initially in 488 (96%) of women. Eighteen women had a successful insertion with a second attempt and one woman required a third attempt because of malfunction of the inserter with the first two attempts. Two (0.4%) women were unable to have a Mirena successfully inserted. Of the 21 unsuccessful first attempts, the most notable reasons for failure included 6 women in whom the IUS expelled immediately, 3 women for whom the cervix would not allow passage of the inserter, and 1 woman with a uterus that was "too small."

Little data is available about rating insertion difficulty in women receiving a 52 mg LNG-releasing IUS. Two separate trials, one in nulliparous women (Suhonen) and another in women age 35-45 years (Dubuisson) both reported that 85% of clinicians rated insertion as easy. However, the proportion that felt insertion was difficult was not detailed. Amongst the nulliparous women reported by Suhonen et al, 21% reported severe pain at insertion although only 13% received cervical anesthesia. A more recent trial of Mirena from 5 centers in Europe included 23% nulliparous women; overall, 2 of 254 (0.8%) had a failed first insertion and both had a successful second insertion attempt, 9.4% required dilation for successful placement, and 86% of clinicians rated insertion as easy (Gemzell-Danielsson).

Of the 81 women in the study by Jensen et al who had a removal in the first year, 1 reported severe pain with removal. All of the devices were able to be removed. However, embedment in the myometrium can occur which may result in a difficult removal. Management of difficult insertion and removal are outlined in Appendix C.

7.1.3 Expulsion

Large trials of the levonorgestrel IUS have reported spontaneous expulsion rates at one year ranging from 3.1% to 4.5% (Luukkainen, Jensen, Andersson 1994), the highest rate of which was reported in parous U.S. women (Jensen). The cumulative expulsion rate by 60 months is 5.8% (Andersson 1994). Expulsion management is outlined in Appendix C.

7.1.4 Pelvic Infection

Older studies suggest an increased risk of PID within the first 20 days after copper IUD insertion (Farley). The absolute risk is low (9.7 cases per 1,000 woman-years in the first 20 days after

insertion), and declines to baseline levels after the first 20 days. Studies with Mirena are different, with some suggestion that Mirena, unlike copper IUDs, may be protective against upper tract infection (Toivonen). There appears to be no increased risk of infection around the time of insertion with Mirena (Andersson 1994). Less than 1% of users have the IUS removed over 5 years because of PID (Andersson 1994). Similar incidence rates are expected for the LNG20. All subjects will be screened for Chlamydia and also for other genital infections as appropriate before study entry.

LNG20 and Mirena do not prevent sexually transmitted disease (STDs), including HIV. Any subject who, at enrollment, feels she is at high risk for STDs (for example, multiple sexual partners) should use a male latex condom every time she has vaginal, oral, or anal sex, and should not enroll in the study. Pelvic infection management is outlined in Appendix C.

7.1.5 Perforation

Uterine perforation is estimated to occur in approximately 1/1000 insertions, regardless of the type of intrauterine device, including Mirena (Sivin; Harrison-Woolwych; Walsh). Perforation management is outlined in Appendix C.

7.1.6 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 Mirena. In a randomized trial of Mirena and a copper IUD, discontinuations for pain unrelated to infection occurred at equal rates for both devices: 1.6 per 100 users in the first year and 4.2 per 100 users cumulatively over 5 years (Andersson 1994). A similar rate of removal (2.4% at 12 months) for pain was found in US women using Mirena (Jensen). Pain may be due to uterine cramping (perhaps related to placement) or ovarian follicular cysts. However, there is no clear data on whether the incidence of functional ovarian cysts is increased in Mirena users as compared to the general population.

7.1.7 Menstrual Changes

Women who use a LNG IUS experience a change in menstrual bleeding patterns. Most commonly, women experience irregular bleeding and spotting in the first 3-6 months after

insertion. The average number of days of bleeding and spotting decline over the first year with an average of less than 2 days of bleeding per month by the end of one year (Andersson 1994). Approximately 20% of women are amenorrheic for a period of 90 days or more by the end of the first year of use (Andersson 1994). In a U.S. study, approximately 80% of Mirena users rated their bleeding as much lighter at the end of 12 months of use compared to 4% of subjects who considered their bleeding to be heavier (Jensen). Approximately 70% of women rated the changes in their bleeding as beneficial.

Hemoglobin values increase with LNG IUS use by an average of 2.4 g/dL at 3 months and 1.8 g/dL at 12 months (Luukkainen). The hemoglobin levels then appear to remain stable with a mean increase of 1.6 g/dL at 5 years (Andersson 1994). The increases are related to starting levels as women with a lower hemoglobin initially experience a greater increase (Luukkainen).

Discontinuation because of bleeding problems is reported to occur in approximately 7.3 per 100 women in the first year and 15 per 100 women cumulatively over 5 years (Andersson 1994). Approximately 4 per 100 women discontinue because of amenorrhea. Such removals may be avoided with better counseling. In a recent US trial, 3.5% of women discontinued Mirena in the first year because of complaints related to bleeding (Jensen). This lower rate may be related to better counseling regarding the expected bleeding or a difference in the subject population. Possible bleeding changes with the LNG20 in this study are not expected to pose a substantial risk to the subject's health but rather an inconvenience.

7.1.8 Systemic Side Effects

Although systemic levonorgestrel levels are very low, women using Mirena do report progestin-related side effects, albeit at very low rates. At 3 months of use, less than 5% of women complain of back pain, headache, nausea, depression, acne or mastalgia (Andersson 1994). The rates of these problems decrease to less than 2% at 60 months. In a randomized trial, weight change over 5 years in Mirena users is identical to copper IUD users (Andersson 1994).

Hormonal and non-hormonal IUD use for more than 7 years is common practice throughout the world. IUDs are commonly removed and a new one reinserted for continuous exposure. No products are labeled anywhere in the world such that continuous exposure for a set number of years is considered unsafe or listed as a warning. Women are also exposed systemically to much

higher doses of hormones with prolonged and continuous use of systemic hormonal contraceptives. Similar to IUDs, no products are labeled anywhere in the world such that continuous exposure for a set number of years is considered unsafe or listed as a warning.

A review paper published in 2007 discussed the known outcomes of prolonged use of the LNG 52 mg IUS, including use of a second and third product. That review article primarily focuses on bleeding pattern changes and continued use into the menopausal transition. Studies on the repeat use of the LNG IUS with second and third consecutive IUSs have shown high continuation rates and low rates of adverse effects. During repeat use of the LNG IUS, the bleeding pattern changes toward an increasing amenorrhea rate (Inki 2007).

As the drug released from hormonal IUSs decreases gradually over time, the drug exposure from one hormonal IUS placed in the uterus for over 7 years will result in a lower hormone exposure compared to insertion of a new IUS.

7.1.9 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).

7.1.10 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. Appropriate imaging studies should be performed to determine the location of the IUS. Missing string management is outlined in Appendix C.

7.1.11 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.

7.1.12 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.

7.1.13 Vaginal Ultrasound

A vaginal ultrasound examination will be performed for women in the endometrial substudy, 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.

7.1.14 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.

7.1.15 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 benefit-risk 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.

7.3.1 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established to conduct reviews of overall safety during study conduct. Members of the IDMC will be chosen based the ability to monitor IUS safety and will be completely independent with no conflicts of interest and no relation to the institutions or centers involved in the study. The composition of members, meeting frequency and specific responsibilities will be outlined in a separate IDMC Charter.

7.4 Pregnancy Assessment

High sensitivity urine pregnancy tests are performed at each study visit. For any positive pregnancy test on IUS treatment or through the 30-Day Safety Follow-up:

- immediately obtain a serum quantitative hCG and
- 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
- any pregnancy occurring on study treatment or identified through the 30-Day Safety Follow-up Visit requires completion of 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 (while the IUS is in the subject and up to and including 7 days after IUS discontinuation) 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 management is outlined in Appendix B.

7.5 Pregnancy Reporting

A pregnancy is considered to have occurred *during the study* if a test or examination confirms a pregnancy while the IUS is being used as a method of contraception by the subject and up to and including 7 days after IUS discontinuation. Pregnancy is not to be reported as an adverse event unless it is an ectopic pregnancy or meets the criteria for a serious adverse event.

Pregnancy Reporting:

- Date of conception up to and including 7 days after IUS discontinuation:
  - Complete Pregnancy Report Form CRF
  - Complete Pregnancy Outcome CRF
  - Complete Pregnancy Narrative (see Study Reference Manual)
- Positive urine pregnancy test at 30-Day Safety Follow-up Visit Date but date of conception more than 7 days after IUS discontinuation:
  - Complete the Pregnancy Narrative
- Pregnancy determined after the 30-Day Safety Follow-up Visit during the 12 month return of fertility follow-up:
  - Complete the Fertility Follow-up section of the Study Follow-Up and Final Status CRF.

7.6 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).

7.7 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.

- 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 30 days after IUS discontinuation (through the 30-Day Safety Follow-up Visit for expulsions of unknown date) 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

7.8 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 (subject is at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received study drug
- Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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

7.9 Clarification of Serious Adverse Events

The following are clarifications of the above definitions of SAEs:

- "Inpatient 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
- "Inpatient hospitalization" 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 the purpose of treatment or observation, the definition of "Inpatient hospitalization" is met. Brief 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

- "Life-threatening" means that the subject was 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
- 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

7.10 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. All SAEs occurring from the beginning of study IUS insertion through 30 days after IUS discontinuation (through the 30-Day Safety Follow-up Visit for expulsions of unknown date) 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 as follows:

- Complete the "Serious Adverse Event Report" form
- Fax the Serious Adverse Event form to Sponsor
- For fatal or life-threatening events, also fax copies of hospital case reports, autopsy reports, and other documents when requested and applicable
- The Sponsor may request additional information from the Investigator to ensure the timely completion of accurate safety reports
- Any fatal or life-threatening events should also be reported immediately by telephone to the Sponsor
- The SAE form should be completed as thoroughly as possible and signed by the Investigator before transmittal to Sponsor. However, submission of SAEs should not be delayed waiting for an Investigator signature. It is also 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 7.12.2 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

7.11 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., electrocardiogram, 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.

7.12 Reporting of Adverse Events

Any AE occurring from the beginning of the IUS insertion procedure until 30 days after IUS discontinuation must be documented in the subject's study records and appropriate CRF.

7.12.1 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
    - Months 1-24:
        - 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)
    - Months 25-121
        - Starting at Month 27 (phone contact), study sites will begin to assess menstrual bleeding/cramping for the prior 3 months (from Month 25; the subject will be asked to characterize her bleeding/cramping pattern for the prior 3 months and compare to when she was not using hormonal contraception prior to study entry)
        - Menstrual bleeding or cramping/pain should also be reported on the general AE CRF if:
            - Bleeding or cramping/pain is indicated as worse in severity or frequency than when the subject was not using hormones on the Bleeding/Cramping Form (verify against Menstrual History)
            - Self-reported by the subject for any months not included in the form (e.g., subject missed last contact so no form was completed) and worse in severity or frequency than when the subject was not using hormones (verify against Menstrual History)

- Bleeding or cramping/pain meets serious criteria (see section 7.8)

7.12.2 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.

7.12.3 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

7.12.4 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**: A condition whereby the consequences of a disease or injury include lingering effects
- **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

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.

7.13 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
  - the IUS was left in place
  - the IUS was removed at the time of the AE but due to a different AE or reason
  - the IUS was already removed prior to the AE start date
  - the AE was a full expulsion
  - the subject was LTFU
- **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 risk for a serious complication

- **IUS Removed for Safety Reasons**: The IUS was removed for an Adverse Event because the subject was at 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

7.14 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.

7.15 Follow-up of Adverse Events and Serious Adverse Events

All AEs and SAEs must be followed through the 30 Day Safety Follow-up Visit, 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.

7.16 Clarification in Reporting of Deaths

All subject deaths (regardless of relationship to study drug) should be reported that occur from the beginning of study IUS insertion through 30 days after IUS discontinuation (or through the 30-Day Safety Follow-up Visit for expulsions of unknown date) while on study protocol up to

and including the follow-up visit. 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 in 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.

7.17 Post-Study Treatment Reporting Requirements

For all enrolled subjects, all AEs and SAEs, regardless of cause or relationship, that occur from the beginning of study IUS insertion through 30 days after IUS discontinuation (through the 30-Day Safety Follow-up Visit for expulsions of unknown date) 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.

7.18 Subject Withdrawal

7.18.1 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). Withdrawal from treatment is not the same as withdrawal from the study, and all subsequent study-related activities described in Sections 6.5 and 6.6 should be completed.

- 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 IUS expulsion (partial or complete)
- 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
    - Investigator determination that it is not in the subject's best interest to continue participation
    - If the subject uses another form of contraception for four consecutive months, or establishes a pattern of intermittent use of other contraception for 4 months out of any 12 month period, the Medical Monitor should be contacted to discuss the subject's continuing participation in the study
- Subjects who have their IUS discontinued should be seen for the 30-Day Safety Follow-up visit unless the expulsion occurred 30 or more days prior, in which case the 30-Day Safety Follow-up visit may be combined with the Early Discontinuation visit

7.18.2 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
- Any subject for whom correct insertion of the assigned IUS is not successful will be withdrawn from the study without further testing or follow-up (except in the case of IUS insertion procedure-related adverse events which should be appropriately assessed and followed as per Section 7.12)

- 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 Early Discontinuation procedures with appropriate 30-Day Safety Follow-up Visit
- 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 Early Discontinuation procedures with appropriate 30-Day Safety Follow-up Visit
- A subject may be discontinued from the study if she relocates to a residence greater than approximately 150 miles from the original study site. The subject may request to be transferred to another study site within 150 miles of her new location (if available). Each request for transfer or discontinuation due to relocation should be reviewed with the Medical Monitor. Any subject being discontinued due to relocation should undergo Early Discontinuation procedures with appropriate 30-Day Safety Follow-up Visit
- 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.

7.18.3 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 randomized or enrolled into the study.

7.18.4 Missed Visits/Contacts and Lost to Follow Up

All reasonable efforts should be made to ensure that enrolled subjects return to the investigational site for all study visits. Any subject who misses a scheduled visit or telephone follow-up call 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 is unsuccessful then future attempts should be made at the time of the next expected study contacts (visits or telephone contact)
    - 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:

- Scheduled study visits or phone contacts are missed for at least 6 months, spanning from the last study contact to the end of the window for the next scheduled visit or phone contact. A subject may be considered lost to follow up after missing two consecutive clinic visits, even if she has been compliant in completing her phone contacts per the protocol
- The 30-Day Safety Follow-up Visit is missed and three documented contacts and a certified letter do not result in a study visit within 30 days of the end of the expected visit window

Subjects designated as lost to follow-up who later resume contact with the site should be requested to have their IUS removed but no other study-related procedures are to be conducted and no study documentation other than IUS accountability is required but clinical documentation of the IUS removal should be made.

7.18.5 Withdrawal of Consent

Subjects expressing a desire to withdraw consent for participation in this study should be asked to return to the clinic for an Early Discontinuation Visit which will include IUS removal if the subject is agreeable. The subject should be advised that this study involves an experimental long-acting drug/device which makes removal of the IUS an important safety aspect of the study discontinuation process. If the subject desires to withdraw consent and is not willing to return to the site for an Early Discontinuation Visit, she should be informed that no further study-related activities will be offered aside from removal of the study IUS if the subject later contacts the site and the study is still ongoing. 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 made directly onto paper source documents and regularly faxed at study clinic visits to [redacted] Data Management and converted into eCRFs. [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., hematology, chemistry, quantative hCG, urine pregnancy, Chlamydia, gonorrhea and Pap evaluations) will be collected utilizing the site's local accredited laboratory (unless performing CLIA-waived tests) with the exception of the plasma levonorgestrel samples which will be analyzed by a central bioanalytical lab. The site will enter the laboratory values for subjects in the clinical trial electronic database. The plasma levonorgestrel sample data from the central bioanalytical lab will be provided to [redacted] at pre-determined intervals during the study. 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 coverted 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. All safety and efficacy data will be stratified by age, parity and BMI for secondary analyses. Prior to implementing the analysis a detailed statistical analysis plan will be written.

9.1 Sample Size

Eligible subjects 16-35 years of age will include approximately 1,600 subjects using LNG20 and 160 subjects using Mirena. Approximately 650 LNG20 and 160 Mirena subjects were randomized at a 4:1 ratio of LNG20 to Mirena. However, the remaining 950 subjects will be assigned to LNG20 only. The estimation of the required number of subjects needed to evaluate the contraceptive efficacy of the LNG20 is based on four assumptions about the annual Pearl Index:

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

Approximately 1,910 women will be enrolled into the study to be assigned to LNG20 or Mirena, with the goal that a minimum of approximately 1,600 LNG20 users and 160 Mirena users are enrolled between the ages of 16 and 35 years. Approximately 650 LNG20 and 160 Mirena subjects were randomized at a 4:1 ratio of LNG20 to Mirena. However, the remaining 950 subjects to be enrolled will only include assignment to LNG20. A cohort of approximately 150

women 36-45 years old will be assigned to LNG20. Enrollment will continue until these minimums are met. The randomization of subjects in the Treatment PK substudy (approximately 60) and the Endometrial Thickness substudy is completed and was enrolled as follows:

- Treatment PK substudy: subjects were assigned by the IVRS separately from the remainder of study subjects based on BMI. Forty non-obese women (BMI<30 kg/m^2) were randomized in a 1:1 ratio to LNG20 and Mirena. Twenty obese women (BMI≥30 kg/m^2) were assigned LNG20
- Endometrial Thickness substudy: subjects were assigned by the IVRS separately from the remainder of study subjects to LNG20

It is expected that 1,600 LNG20 subjects (16-35 years old) will provide at least 10,000 woman-months of exposure in the first two years, at least 350 woman-years of use in the final year of the study (year 10) for efficacy analysis of the LNG20.

The number of subjects to be randomized to the Mirena arm is not based on contraceptive efficacy but on providing an informative comparator.

Subjects who discontinue treatment for any reason 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 age and outcome.

Modified Intent To Treat (MITT): All LNG20 subjects between 16 and 35 years of age at study entry for whom the assigned IUS is successfully placed in the uterus and for whom there is at least one assessment of pregnancy status after inserting the IUS.

Per Protocol (PP): 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 for the overall population and by IUS type.

9.4 Demographic and Other Subject Characteristics

Subject demographics and pre-treatment characteristics will be summarized by treatment group and overall. No statistical tests will be performed to compare demographics between treatment groups.

9.5 Extent of Exposure

Exposure to study IUS will be summarized by treatment group and overall 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 active study treatment period. Pre-trial medications include any medications taken within seven days (30 days for anticoagulants) of enrollment. 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 Pearl Index at two years for women in the MITT population who received LNG20 is the primary efficacy endpoint. Pearl indices and life table pregnancy analyses will be presented by treatment group using the MITT population

The Pearl Index and 95% confidence interval will be used to establish efficacy for 2 years of use. Pregnancies in the MITT population to be included in the primary analysis are those that occurred while a study IUS was in place (determined by ultrasound and medical assessments) or

following unrecognized IUS expulsion. For clarification, if a pregnancy occurs in a woman with a known date of IUS expulsion, and that pregnancy occurred while not on study treatment or up to and including 7 days after IUS discontinuation, that pregnancy will not be counted in the primary analysis. Cycles (defined as 28-day intervals) where backup methods of contraception were used will be excluded from the primary analysis of the Pearl Index unless the subject became pregnant in that cycle. To establish the efficacy of LNG20 for 2 years of use, acceptable precision of the Pearl Index must be reached during year 1 and, separately, during year 2, where acceptable precision is defined as the upper bound of the 95% confidence interval being no more than 1 unit above the point estimate of the Pearl Index. This hierarchical approach will not require adjustment to the acceptable precision required for the confidence interval of the Pearl Index.

9.8 Key Secondary Outcomes

The Pearl Index analysis described above for the primary outcome will also be performed for use during years 3, 4, 5, 6, 7, 8, 9 and 10 using the MITT population. The Pearl Index will be calculated for use during years 3, 4, 5, 6, 7, 8, 9 and 10 with a goal of each having acceptable precision (defined as the upper bound of the 95% confidence interval being no more than 1 unit above the point estimate). Other Secondary Outcomes

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

- **Pregnancy Rates**

  Pearl indices and life table pregnancy analyses will also be prepared for the PP population during years 3, 4, 5, 6, 7, 8, 9 and 10 unless the populations are essentially the same as the MITT population. Kaplan-Meier methods will be used to estimate the cumulative pregnancy percentage for years 1 through 10 for each treatment group using the MITT population.

- **IUS Continuation Rates**

  Cumulative IUS continuation rates at 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years and 10 years will be summarized for each treatment group, as applicable, using Kaplan-Meier methods.

- **IUS Expulsion Rates**

Cumulative IUS expulsion rates at 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years and 10 years will be summarized for each treatment group, as applicable, using Kaplan-Meier methods.

- **IUS Safety-Related Removal Rates**

  Cumulative IUS safety-related removal rates at 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years and 10 years summarized for each treatment group, as applicable, using Kaplan Meier methods.

- **Vaginal Bleeding Patterns**

  Vaginal bleeding patterns (none, spotting, and light, normal, or heavy flow [bleeding]) will be summarized by incidence and duration of bleeding. Baseline vaginal bleeding is recorded on the Menstrual History CRF based on menstrual characteristics when not using hormonal contraception.

  Based on 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.

- **Dysmenorrhea**

  Dysmenorrhea (none, mild, moderate, or severe) will be summarized by the number and percentage of days with a particular pattern during each 84 and 90 day interval after enrollment through Month 24. After Month 24 dysmenorrhea will be summarized from the Adverse Events CRF. In addition, dysmenorrhea changes from baseline will be summarized using shift tables. Baseline dysmenorrhea is recorded on the Menstrual History CRF based on menstrual characteristics when not using hormonal contraception.

- **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:

  - Difficult insertion or removal procedure;
  - Perforation of the uterus;
  - Dysmenorrhea;
  - Low abdominal pain (not classified as dysmenorrhea);
  - Uterine infection (including PID); and
  - Other urogenital infections

- **Pregnancy Outcomes**

  Pregnancy outcomes will be summarized by treatment group using the MITT population as well as listed by subject.

- **Fertility Rates**

  Those women desiring pregnancy after leaving the study will be contacted every three months up to one year after IUS discontinuation to record any pregnancy. Kaplan-Meier methods will be used to estimate the probability of pregnancy over time.

- **Menses After IUS Discontinuation**

  Those women who elect to use a non-hormonal contraceptive method or no contraception (including those desiring pregnancy) will be followed monthly for up to 3 months after IUS removal/expulsion for the occurrence of menses following IUS discontinuation. Women who do not menstruate within 3 months following IUS discontinuation will be referred for appropriate evaluation and continue to be followed monthly until menses has occurred or a diagnosis for the cause of the secondary amenorrhea has been established. Kaplan-Meier methods will be used to estimate the probability of the return of menses over time.

- **Plasma Levonorgestrel Levels**
  - Levels over the lifespan of IUS use

    Levonorgestrel plasma levels will be obtained for all subjects at 6 months intervals and at IUS discontinuation visit beginning with Month 36 until Protocol Version 9 when thereafter, levonorgestrel plasma levels will be obtained in all subjects at IUS discontinuation and also annually in all women enrolled prior to 31May2011. Descriptive statistics will be presented at each visit to summarize the plasma levonorgestrel levels over time.
  - Levels following removal

    Levonorgestrel plasma levels obtained at 24 and 48 hours and 7 and 14 days following removal after the entire duration of use will be summarized.
  - Pharmacokinetic subset

    Levonorgestrel plasma levels obtained in the PK subset will be summarized at each visit. Descriptive statistics will be presented for each visit and a graph will be presented of the mean levonorgestrel serum levels over time.
  - IUSs that are removed or expelled during the study

    Analysis of a sampling of retained IUSs will be summarized.
- **Endometrial Thickness**

  Changes in endometrial thickness after one, five and 10 years will be compared to baseline.
- **Other Outcomes**

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

9.9 Study Stopping Rules Based on Efficacy

Overall pregnancy rates for the study will be monitored continuously by the Sponsor and IDMC. If the overall pregnancy rate for subjects who received the LNG20 in the MITT population exceeds 3%, the study will be discontinued.

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 diseases (STDs). 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 by [redacted] Up to 30 sites in the US will participate in this study to enroll approximately 1,910 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 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. For those subjects under 18 years old informed consent must also be obtained and documented from a parent or legal guardian. 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 2 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 should understand 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.

11. REFERENCES

Andersson K, Batar I, Rybo G. Return to fertility after removal of a levonorgestrel-releasing intrauterine device and Nova-T. Contraception. 1992;46:575–584.

Andersson K, Odlind V, Rybo G. Levonorgestrel-releasing and copper-releasing (Nova T) IUDs during five years of use: A randomized comparative trial. Contraception 1994;49:56-72.

ARHP *Clinical Proceedings,* September 2004.

Backman T, Rauramo I, Huhtala S, Koskenvuo M. Pregnancy during the use of levonorgestrel intrauterine system. Am J Obstet Gynecol 2004;190:50-4.

Belhadj H, Sivin I, Diaz S, et al. Recovery of fertility after use of the levonorgestrel 20 mcg/d or copper T 380Ag intrauterine device. Contraception. 1986;34:261–267.

Benda N, Gerlinger C, van der Meulen A, and Endrikat J. Sample Size Calculation for Clinical Studies on the Efficacy of a New Contraceptive Method. Biometrical Journal 46 (2004) 1, 141–150.

FDA. Medical Review(s): in Summary Basis of Approval (SBA) for Skyla (Levonorgestrel-releasing intrauterine system). 2012.

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR).

Dubuisson JB, The Mirena Study Group, Mugneir E. Acceptability of the levonorgestrel-releasing intrauterine system after discontinuation of previous contraception: results of a French clinical study in women aged 35 to 45 years. Contraception 2002;66:121-8.

Farley TM, Rosenburg MJ, Rowe PJ, Chen JH, Meirik O. Intrauterine devices and pelvic inflammatory disease: an international perspective. Lancet 1992;339:785-8.

Farmer M, Webb A. Intrauterine device insertion-related complications: can they be predicted? J Fam Plann Reprod Health Care 2003;29:227-31.

Ganer H, Levy A, Ohel I, et al. Pregnancy outcome in women with an intrauterine contraceptive device. Am J Obstet Gynecol 2009; 201:1.e1-1.e4.

Gemzell-Danielsson, K, Schellschmidt, I,Apter, D. A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose levonorgestrel-releasing intrauterine contraceptive systems and Mirena. Fertil Steril (epub 2012 Jan 3 ahead of print).

Harlap S, Kost K, Forrest JD. Preventing pregnancy, protecting health: a new look at birth control choices in the U.S. The Alan Guttmacher Institute, 1991:1-129.

Harrison-Woolrych M, Ashton J, Coulter D. Uterine perforation on intrauterine device insertion: is the incidence higher than previously reported? Contraception 2003;67:53-6.

Heikinheimo O, Inki P, Schmelter T, Gemzell-Danielsson K. Bleeding pattern and user satisfaction in second consecutive levonorgestrel-releasing intrauterine system users: results of a prospective 5-year study. Hum Reprod. 2014 Jun; 29(6): 1182–1188.

Hidalgo, M.M., Hidalgo-Regina, C., Bahamondes, M.V. et al. Serum levonorgestrel levels and endometrial thickness during extended use of the levonorgestrel-releasing intrauterine system. Contraception 2009;80:84–9.

Inki P. Long-term use of the levonorgestrel-releasing intrauterine system. Contraception 2007;75(Suppl):S161-6

Jensen J, Nelson A, Costales A. Subject and clinician experience with the levonorgestrel-releasing intrauterine system. Contraception 2008;77:22-9.

Kavanaugh ML, Jerman J, Finer LB. Changes in use of long-acting reversible contraceptive methods among U.S. women, 2009-2012. Obstet Gynecol 2015:126:917-27.

Lewis RA, Taylor D, Natavio MF, et al. Effects of the levonorgestrel intrauterine system (LNG-IUS) on cervical mucus quality and sperm penetration (abstract). Fertil Steril 2009;92:S27.

Luukkainen T, Allonen H, Haukkamaa M, et al. Effective contraception with the levonorgestrel-releasing intrauterine device: 12-month report of a European multicenter study. Contraception 1987;36:169-79.

Marions L, Lövkvist L, Taube A, Johansson M, Dalvik H, Øverlie I. Use of the levonorgestrel releasing-intrauterine system in nulliparous women--a non-interventional study in Sweden. Eur J Contracept Reprod Health Care. 2011;16:126-34.

Mosher WD, Jones J. Use of Contraception in the United States: 1982-2008. National Center for Health Statistics. Vital Health Stat 23 (29). 2010.

Ronnerdag, M. and Odlind, V. Health effects of long-term use of the intrauterine evonorgestrel releasing system. A follow-up study over 12years of continuous use. Acta Obstet Gynecol Scand 1999;78:716–21

Rowe P, Farley T, Peregoudov A, Piaggio G, Boccard S, Landoulsi S, Meirik). Safety and efficacy in parous women of a 52-mg levonorgestrel-medicated intrauterine device: a 7-year randomized comparative study with the TCu380A. Contraception 2016;93:498-506.

Salem, R. "New Attention to the IUD: Expanding Women's Contraceptive Options To Meet Their Needs." *Population Reports*, Series B, No. 7. Baltimore, Johns Hopkins Bloomberg School of Public Health, The INFO Project, February 2006.

Sitruk-Ware R. Contraception: an international perspective. Contraception 2006;73:215-22.

Sivin I, Stern J, Coutinho E, et al. Prolonged intrauterine contraception: a seven-year randomized study of the levonorgestrel 20 mcg/day (LNg 20) and the Copper T380 Ag IUSs. Contraception 1991;44:473-80.

Suhonen S, Haukkamaa M, Jakobsson T, Rauramo I. Clinical performance of a levonorgestrel-releasing intrauterine system and oral contraceptives in young nulliparous women: a comparative study. Contraception 2004;69:407-12.

Toivonen J, Luukkainen T, Allonen H. Protective effect of intrauterine release of levonorgestrel on pelvic infection: three years' comparative experience of levonorgestrel- and copper-releasing intrauterine devices. Obstet Gynecol 1991;77:261-4.

Walsh T, Grimes D, Frezieres R, Nelson A, Bernstein L, Coulson A, et al. Randomized controlled trial of prophylactic antibiotics before insertion of intrauterine devices. Lancet 1998;351:1005-8.

Wu JP, Pickle S. Extended use of the intrauterine device: a literature review and recommendations for clinical practice. Contraception 2014;89:495-503.

APPENDIX A: SCHEDULE OF EVENTS LNG20

Assessments[1]	Enrollment	Visit	Contact	Visit	Visit	Visit	Visit	Contact	Visit	Contact	Visit	Term/Early Discontinuati	30 Day Safety FU	Continued Follow-up
	Day 1	Month 1, 3, 6, 18	Month 9, 15, 21	Month 12	Month 24	Month 36, 48, 72, 84, 96*†, 108*	Month 60	Month 27, 33, 39, 45, 51, 57, 63, 69, 75, 81, 87, 93, 99*, 105*, 111*	Month 30, 42, 54, 66, 78, 90, 102*, 114*	Month 93, 117*	Month 120*	Month 121*[7]	30-43 days	
Informed Consent	X													
Demographic Information	X													
Medical/Medication[2] History	X													
Breast Exam[3]	X			X	X	X	X				X	X[9]		
Vital Signs (wt, BP)	X	X		X	X	X	X		X		X	X	X	
Height	X													
Pelvic Exam with Pap	X[4]			X[4]	X[4]	X[4]	X[4]				X	X[4,9]		
Chlamydia/Gonorrhea	X[5,6]	X[6]		X[5,6]	X[5,6]	X[5,6]	X[5,6]		X[6]		X	X[5,6,7]	X[6]	
Urine Pregnancy	X[8]	X		X	X	X	X		X		X	X	X	
Hemoglobin	X			X			X				X	X[9]		
Serum Chemistry[10]	X													
Confirm Eligibility	X													
Assign IUS in IVRS	X													
Insertion of IUS	X													
AE Related to IUS Procedure	X											X		
Instruct/Dispense Daily Diary	X	X		X	X	X	X		X		X			
Counsel HIV/STD Risks	X													
Review Diary Compliance		X	X	X	X	X	X	X	X	X	X	X		
Bleeding/Cramping Form						X	X	X	X	X	X	X		
Review Contraception Use[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Sexual Partner Status[4]		X	X[12]	X	X	X	X	X[12]	X	X[12]	X	X		
Review of Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review Concomitant Meds		X	X	X	X	X	X	X	X	X	X	X	X	
Plasma Levonorgestrel						X[††]	X[††]		X[††]			X[††,13]		
Verify IUS Presence[14]		X		X	X	X	X		X		X	X		
Ask About Relocation or Early Discontinuation Plans		X	X	X	X	X	X	X	X	X	X			
Removal of IUS												X		
Contraception Counseling			X[15]			X		X[15]		X[15]	X	X[16]	X	
Schedule/Confirm Next Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X[17, 18]

[1] LNG20 16-35 year old enrollment group only
[2] To occur ± 14 days of clinic visit (±7 days for Months 1, 3 and 121)
[3] Medications for 7 days prior to enrollment and anticoagulants for 30 days
[4] Include any clinically indicated physical exam
[5] Pap test per protocol section 6.11 guidelines
[6] Chlamydia testing for all subjects ≤ 25 years old
[7] Both tests if change in sexual partner since last tested or last visit
[8] If not tested within the previous 6 months
[9] Urine pregnancy if not done on same day prior to insertion
[10] If not done within the last 3 months
[11] Includes creatinine, AST, ALT, bilirubin
[12] Review any other contraception use
[13] If change in sexual partner is noted during contact bring in for unscheduled G/C testing prior to next clinic visit
[14] Not required if Early Discontinuation <36 months
[15] By palpation or visualization (ultrasound evaluation if missing strings at first and annual visits)
[16] For contact or visit prior to Month 96 for LNG20 36-45 year old group and Month 121 for LNG20 16-35 year old group or Early Discontinuation discuss contraception options for discontinuation visit
[17] Initiation of primary method of contraception when possible
[18] Appropriate monthly contact by phone or clinic visit to follow ongoing AEs and return to menses. If no return to menses within 3 months of IUS removal/expulsion, refer for evaluation and continue follow-up until diagnosis is made
[†] For women desiring pregnancy follow by phone contact every 3 months up to one year based on date of IUS discontinuation
[*] LNG20 36-45 year old group see Month 121/ED procedures
[††] LNG20 36-45 year old group only

SCHEDULE OF EVENTS: MIRENA

Assessments[1]	Enrollment	Visit	Contact	Visit	Visit	Visit	Contact	Visit	Contact	Termination/ Early Discontinuation	Safety FU	Combined FU
	Day 1	Months 1, 3, 6, 18	Months 9, 15, 21	Month 12	Month 24	Months 36, 48	Months 27, 33, 39, 45, 51,	Months 30, 42, 54	Month 57	Month 60	30-43 days	
Informed Consent	X											
Demographic Information	X											
Medical/Medication[2] History	X											
Breast Exam[3]	X			X	X	X				X		
Vital Signs (wt, BP)	X	X		X	X	X		X		X	X	
Height	X											
Pelvic Exam with Pap	X[4]			X[4]	X[4]	X[4]				X[4]		
Chlamydia/Gonorrhea	X[5,6]	X[6]		X[5,6]	X	X[5,6]		X[6]		X[5,6,7]	X[6]	
Urine Pregnancy	X[8]	X		X	X	X		X		X	X	
Hemoglobin	X			X						X		
Serum Chemistry[9]	X											
Confirm Eligibility	X											
Assign IUS in IVRS	X											
Insertion of IUS	X											
AE Related to IUS Procedure	X											
Instruct/Dispense Daily Diary	X	X		X	X	X		X				
Counsel HIV/STD Risks	X				X							
Review Diary/Compliance		X	X	X	X	X	X	X	X	X		
Bleeding/Cramping Form						X	X	X	X	X	X	
Review Contraception Use[10]	X	X	X	X	X	X	X	X	X	X	X	
Sexual Partner Status[9]		X	X[11]	X	X	X	X[11]	X	X[11]	X		
Review of Adverse Events	X	X	X	X	X	X	X	X	X	X	X	
Review Concomitant Meds		X	X	X	X	X	X	X	X	X	X	
Plasma Levonorgestrel						X		X		X[12]		
Verify IUS Presence[13]		X		X	X	X		X		X		
Removal of IUS										X		
Ask About Relocation or Early Discontinuation Plans		X	X	X	X	X	X	X	X			
Contraception Counseling									X[14]	X[15]	X	
Schedule/Confirm Next Visit	X	X	X	X		X	X	X	X	X	X[16]	X[16,17]

[1] To occur ±14 days of scheduled Month (±7 days for Months 1 and 3)
[2] Medications for 7 days prior to enrollment and anticoagulants for 30 days
[3] Include any clinically indicated physical exam
[4] Pap test per protocol section 6.11 guidelines
[5] Chlamydia testing for all subjects ≤ 25 years old
[6] Both tests if change in sexual partner since last tested or last visit
[7] If not tested within the previous 6 months
[8] Urine pregnancy if not done on same day prior to insertion
[9] Includes creatinine, AST, ALT, bilirubin
[10] Review other contraception use
[11] If change in sexual partner is noted during contact bring in for unscheduled G/C testing prior to next clinic visit
[12] Not required if Early Discontinuation <36 months
[13] By palpation or visualization (ultrasound evaluation if missing strings at first and annual visits)
[14] For contact prior to Month 84 Term/ED discuss contraception options for discontinuation visit
[15] Initiation of primary method of contraception when possible
[16] Appropriate monthly contact by phone or clinic visit to follow ongoing AEs and return to menses. If no return to menses within 3 months of IUS removal/expulsion, refer for evaluation and continue follow-up until diagnosis is made
[17] For women desiring pregnancy follow by phone contact every 3 months up to one year

APPENDIX B: 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 section.

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.

APPENDIX C: 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 Pratt 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 but no other types of dilators are permitted.
  - 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 annual 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.
- If the IUS has been expelled or must be removed, the subject cannot receive another IUS and must be discontinued from the study.

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 and the subject discontinued from the study.
- The subject cannot receive another IUS through the study.

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
- Use of alligator forceps (or comparable instrument)
- Use of cervical anesthesia to make manipulation more tolerable

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.

APPENDIX D: 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, Protocol Synopsis	Indication Date and version # changed Changed Medical Officer	Indication changed to extension to 10 years The date and version # changed due to this revision Added [redacted]
Protocol Synopsis Study Objectives, Study Design, Other Secondary Outcome Measures, Statistical Methods; Protocol Sections 2.2, 3.1, 3.2.3, 6.10.2, 9.9	Revised Study Objectives to measure changes in endometrial thickness in a subset of 60 subjects based on transvaginal ultrasonography at 1, 5 and 10 years of LNG20 use PK sampling plan revised to annual plasma levonorgestrel levels of all subjects enrolled prior to 31May2011 and for all subjects at IUS discontinuation after Month 36 starting with this amendment Elimination PK substudy revised to start at end of full duration of product use (121 months) Duration of use for 36-45 year old non-efficacy group limited to 8 years.	Extension of the protocol intended duration of use from 8 years to 10 years PK sampling plan revised [redacted] LNG20 Efficacy group now extended to 121 months of use Discontinuing LNG20 36-45 year old enrollment group at 8 years because their age at discontinuation will be 43 to 53 years old and therefore unlikely to require contraception.

Protocol Synopsis Planned Study Dates, Duration of Subject Participation, Duration of Study Center Participation, Protocol Section 2	Changed Planned Study Dates	Extension of the protocol intended duration of use from 8 years to 10 years
Protocol Synopsis Study Design, Protocol Section 3.1, 6.4	Added study assessments at Months 102, 108, 114, 120, 121	Extension of the protocol intended duration of use from 8 years to 10 years
Protocol Synopsis Study Design, Dosing Regimen, Protocol Sections 3.1, 5, 6.6	Added treatment discontinuation for LNG20 16-35 year old subjects at Month 121 and for LNG20 16-35 year old subjects at Month 96	Extension of the protocol intended duration of use from 8 years to 10 years for LNG20 subjects only. Month 121 added to ensure a complete duration of use through 10 years. Discontinuing LNG20 36-45 year old enrollment group at 8 years because their age at discontinuation will be 43 to 53 years old and therefore unlikely to require contraception.
Protocol Synopsis Study Design, Other Secondary Outcome Measures, Protocol Sections 2.2, 3.1, 3.2.3, 4.4.3, 6.10.3	Levonorgestrel sampling after IUS removal revised to start at Month 121	Extension of the protocol intended duration of use from 8 years to 10 years
Protocol Synopsis Key Secondary Outcome Measures, Statistical Methods, Protocol Sections 3.2.2, 9.1, 9.8	Added years 8, 9 and 10 to efficacy determination Removed requirement for acceptable Pearl Index	Extension of the protocol intended duration of use from 8 years to 10 years [redacted]

Protocol Synopsis Other Secondary Outcome Measures, Protocol Sections 3.2.3, 9.9	Revised cumulative pregnancy rates to be determined through year 10 Added years 9 and 10 for LNG20 subjects only for IUS continuation rates, IUS expulsion rates and IUS safety-related removal rates	Extension of the protocol intended duration of use from 8 years to 10 years Extension of the protocol intended duration of use from 8 years to 10 years
Protocol Synopsis Sample Size, Protocol Section 9.1	Revised sample size	Extension of the protocol intended duration of use from 8 years to 10 years with concomitant additional subject dropouts
Protocol Section 1.1.1	Revised approved duration of use for Liletta® from 3 to 4 years	Liletta (LNG20) approved for extension to 4 years of use in 2017
Protocol Section 6.4	Revised Bleeding/Cramping Form, hemoglobin, plasma levonorgestrel collection visits and breast exam, pelvic exam, Pap testing and STD testing schedule	Extension of the protocol intended duration of use from 8 years to10 years
Protocol Section 6.5	Added study contacts at Months 99, 105, 111 and 117, and revised Bleeding/Cramping Form collection visits Added contact with LNG20 subjects approaching Year 10 discontinuation to notify them of option of extending use to 10 years	Extension of the protocol intended duration of use from 8 years to 10 years Extension of the protocol intended duration of use from 8 years to 10 years
Protocol Section 7.1.1	Added summary of release rate data of LNG20 projected to 10 years	Provided to assess the risk of pregnancy beyond 8 years due to extension of the study to 10 years duration of use
Protocol Section 7.12.1	Revised bleeding/cramping form completion duration to 121 months	Extension of the protocol intended duration of use from 8 years to 10 years
Protocol Section 9.1	Increased dropout rate	Extension of the protocol intended duration of use from 8 years to 10 years

Protocol Section 11	Added references	Additional references provided for Section 7.1.1
Appendix A, Schedule of Events	Revised Schedule of Events	Additional time points and events were added to extend the study to 10 years duration of use for LNG20 16-35 year olds and discontinue LNG20 36-45 year olds at 8 years duration of use