NCT02882191

STUDY PROTOCOL

Evaluation of the Effectiveness, Safety and Tolerability of LevoCept (Levonorgestrel-Releasing Intrauterine System) for Long-Acting Reversible Contraception

DOCUMENT DATE: 18 Oct 2017

CONTRAMED

Review & Approval:

Name	Position	Signature	Date
[redacted]			

Clinical Investigation Plan CMDOC – 0022 Version 4.0 / 18 Oct 2017 Attached 47 pages

DOCUMENT REVISION HISTORY

Rev.	Description	Originator	Effective Date
A	Initial Release	[redacted]	6.8.16
B	Revisions based on Investigator review		10.14.16
C	Amendment V 2.0 / 09 Feb 2017		2.14.17
D	Amendment V 3.0 / 30 Mar 2017		3.30.17
E	Amendment V4.0 /		10.18.17

Evaluation of the Effectiveness, Safety and Tolerability of LevoCept (Levonorgestrel-Releasing Intrauterine System) for Long-Acting Reversible Contraception

Protocol Number:	CMDOC-0022
IND #:	129805
Version / Date:	4.0 / 18 October 2017
Sponsor:	ContraMed, LLC 900 E. Hamilton Avenue, Suite 100 Campbell, CA 95008 [redacted]
Principal Investigator:	**David Turok, MD** Professor Obstetrics and Gynecology University of Utah School of Medicine
Medical Monitor:	**Scott E. Eder, MD FACOG** Medical Director, SynteractHCR, Inc. [redacted]

Investigator's Agreement

I have received a copy of the protocol number CMDOC-0022, Evaluation of the Effectiveness, Safety and Tolerability of LevoCept (Levonorgestrel -Releasing Intrauterine System) for Long-Acting Reversible Contraception, Version 3.0, dated 30 March 2017 from ContraMed. I/we agree to the conditions as set out in this protocol and fully accept that any change requires prior approval from ContraMed. Additionally, I/we agree to carry out all terms of this protocol in accordance with ICH Guidelines; all applicable US Regulations (21 CFR parts 50, 54, 56 and 312) and Good Clinical Practice Guidelines, as applicable. Finally, I/we will ensure that the investigational product will be used only as described in this protocol.

The information contained in this protocol is provided to me in confidence, for review only by myself, the Independent Ethics Committee / Investigational Review Board authorized to review and approve the study at this study site, the designated research staff participating in this clinical study, and applicable regulatory agencies.

I/we understand that the information/technology contained in this protocol is proprietary and may not be disclosed to any other party, in any form, without prior authorization from ContraMed, except to the extent necessary to obtain informed consent from potential study participants.

Investigator's Name (print)	
Investigator's Signature	Date(DD/MMM/YYYY)

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REVISION HISTORY

Version	Date	Justification for Revision
1.0	18 Aug 2016	Initial version
2.0	09 Feb 2017	1. Incorporates feedback provided by investigational sites from the Investigator's meeting 2. Provides additional clarity 3. Administrative changes
3.0	30 Mar 2017	Incorporates changes based on FDA feedback
4.0	18 Oct 2017	Add subject contact at the end of each 28-day cycle post the 52 Week visit. Separated out the exit visits from the regular visits to add clarity.

INVESTIGATIONAL PLAN SUMMARY

Title:	Evaluation of the Effectiveness, Safety and Tolerability of LevoCept (Levonorgestrel-Releasing Intrauterine System) for Long-Acting Reversible Contraception
Protocol #:	CMDOC-0022 Version 4.0 / 18 October 2017
Device Name:	LevoCept Intrauterine Contraceptive; Levonorgestrel-Releasing Intrauterine System (referred to as LevoCept or Study Device throughout this document)
Study Design:	Prospective, multi-center, single-arm, open-label, Phase II clinical study
Study Purpose:	To evaluate the effectiveness, device placement, safety, and tolerability of LevoCept to support commencing a Phase III Clinical Study
Study Duration:	Subject enrollment will take approximately 5 months. Each subject will be followed for 12 months after device placement for the protocol endpoints, and then every 6 months thereafter for up to 24 additional months for those subjects who wish to continue study device use.
Enrollment:	Up to 250 subjects will be consented, screened and have LevoCept placed, with a goal to have 2240 evaluable cycles at 12 months. It is planned that 225 of the 250 subjects will be within the 18-35 year age range, with a total of 2015 evaluable cycles. The remaining 25 subjects will be within the 36-40 year age range.
Investigational Site Information:	This study will be conducted at approximately 16 centers in the U.S.
Follow-up:	Physical assessment (office visit) will occur at weeks 6, 13, 26 and 52 after placement, with monthly contact. For those subjects who wish to continue study device use after 12 months, follow-up office visits will occur every 6 months with contact at the end of each 28-day cycle beginning after the 52-week visit. Additional visits will be conducted if necessary for safety issues. <u>Follow-up after early study device removal:</u> Subjects requesting LevoCept removal to become pregnant will be followed for either; six (6) months, until they decide to no longer try to conceive or they become pregnant, whichever comes first. All subjects in whom LevoCept is removed, for any reason, will be required to use an alternative contraceptive for the first two weeks following removal. Hormonal contraceptive pills will be reimbursed by the sponsor as a contraceptive option during this

time unless the subject has a MEC category 4 condition precluding their use.

Study Population: Pre-menopausal women ages 18–40, at risk for pregnancy, who are interested in using only this intrauterine contraceptive for birth control will be eligible for this study. Subjects must provide written informed consent and meet the study subject selection criteria without any exclusions as outlined in the Clinical Investigation Plan (CIP).

Primary Effectiveness Outcome:

The primary outcome measure is effectiveness, evaluated as the absence of pregnancy with failures calculated by the Pearl Index and life-table analysis. All evaluable cycles prior to discontinuation or planned removal will be included in the primary analysis of effectiveness.

Safety and Other Outcome Measures:

Safety and other outcome measures include:
Study Device Placement:

- Ease of placement
- Placement success

Safety:

- Serious Adverse Events
- Adverse Events

Tolerability:

- Bleeding and spotting patterns
- Discontinuation rate and reasons for discontinuation

Subject Selection Criteria

INCLUSION CRITERIA
Subject must meet all of the following criteria to participate in this study:

1. Between 18-40 years of age at the time of study initiation;
   1.1 Enrollment will be targeted for 225 subjects aged 18-35 (for safety and effectiveness analyses) and an additional 25 subjects aged 36-40 (for safety only) (note: all subjects will be included in the analysis for device placement and tolerability);
2. Pre-menopausal, as determined by regular menstrual cycle (28 ± 7 days) for the last 3 months;
   2.1 Based on patient history, when not on hormonal contraceptives;
3. Sexually active with a male partner who has not had a vasectomy;
4. Reasonably expected to have coitus at least once monthly during the study period.

5. In a mutually monogamous relationship of at least 3-6 months duration;
6. Seeking to avoid pregnancy for the next 12 months;
7. Willing to use the study device as the sole form of contraception;
8. Willing to accept a risk of pregnancy;
9. Subjects who are age 21 or older, at time of informed consent, must have a normal PAP or ASC-US with negative high risk HPV test result within the appropriate screen timeframe, and prior to LevoCept insertion;
10. Able and willing to comply with all study tests, procedures, assessment tools and follow-up; and
11. Able and willing to provide and document informed consent and Authorization for Release of Protected Health Information (PHI).

EXCLUSION CRITERIA

A subject will be excluded from participating in the study if **any** of the following conditions apply:

1. Known or suspected pregnancy; or at risk for pregnancy from unprotected intercourse earlier in current cycle;
2. Subject who anticipates separation from her partner for more than 1 cycle within the next 12 months;
3. A previously inserted IUD that has not been removed by the time LevoCept is placed;
4. History of previous IUD complications*, such as perforation, expulsion, infection (pelvic inflammatory disease) or pregnancy with IUD in place.*;
5. Injection of hormonal contraceptive (e.g., Depo-Provera) within the last 10 months;
   5.1 Must have had 2 normal menstrual cycles since the last injection;
6. Planned use of any non-contraceptive estrogen, progesterone or testosterone any time during the 12 months of study participation;
7. Postpartum, prior to a minimum of 6 weeks and complete uterine involution;
8. Exclusively breastfeeding before return of menses; Lactating women will be excluded unless they have had have had two normal menstrual periods prior to enrollment.
   8.1 Must have had 2 normal spontaneous menstrual cycles since delivery
9. Unexplained abnormal uterine bleeding (suspicious for serious condition), before evaluation; Immediately post-septic abortion or puerperal sepsis (must wait a minimum of 3 months);
10. Severely heavy or painful menstrual bleeding;
11. Suspected or known cervical, uterine or ovarian cancer, or unresolved clinically significant abnormal pap smear requiring evaluation or treatment.
12. Any history of gestational trophoblastic disease with or without detectable elevated ß-hCG levels, or related malignant disease without an intervening normal pregnancy;
13. Any congenital or acquired uterine anomaly that may complicate IUD placement, such as:
    13.1 Submucosal uterine leiomyoma

13.2 Asherman's syndrome
13.3 Pedunculated polyps
13.4 Bicornuate uterus
13.5 Didelphus or uterine septa

14. Any distortions of the uterine cavity (e.g. fibroids), in the opinion of the investigator, likely to cause issues during insertion, retention or removal of the IUD;
15. Known anatomical abnormalities of the cervix such as severe cervical stenosis, prior trachelectomy or extensive conization that, in the opinion of the investigator would prevent cervical dilation and study device placement;
16. Current or recent (within the last 3 months) untreated acute cervicitis or vaginitis ;
17. Known or suspected breast cancer or other progestin-sensitive cancer now or in the past;
18. Known acute liver disease or liver tumor;
19. Subjects who have an established immunodeficiency;
20. High risk for STDs (e.g., multiple sexual partners);
21. Known or suspected HIV infection or clinical AIDS;
22. Known intolerance or allergy to any component of the LevoCept system; including nickel, silicone or tantalum;
23. Subject had LevoCept placed previously or had 2 attempts at placement;
24. Known or suspected alcohol or drug abuse within 12 months prior to the screening visit;
25. Any general health or behavioral condition that, in the opinion of the Investigator, could represent an increased risk for the subject or would render the subject less likely to provide the needed study information.
26. Subject is currently participating or has participated in another clinical study involving another investigational agent within 30 days of the planned LevoCept insertion date or is planning participation in another clinical trial with an investigational agent within 52 weeks (visit 6) after insertion.

LevoCept Insertion Timing

The following must be followed prior to LevoCept insertion to insure adequate contraception coverage:

Subjects Using Any Hormonal Birth Control Method

Subjects using any hormonal birth control method can have LevoCept placed on any day of the menstrual cycle. If the insertion occurs in the first 7 days of the cycle, the hormonal contraception can be discontinued after insertion. If the insertion occurs after the first 7 days of the menstrual cycle, the subject should continue using hormonal contraception for an additional 7 days.

- Subjects using an implant (Implanon/Nexplanon) who have regular cycles, LevoCept should be inserted within seven days of onset of menses and the implant may be removed the same day.

- Subjects using an implant (Implanon/Nexplanon) who have irregular cycles or amenorrhea, LevoCept should be inserted and the implant should be removed seven days after IUD inserted
- Subjects using an implant (Implanon/Nexplanon) with regular cycles but who are beyond seven days of menses, LevoCept may be inserted but removal of implant should occur after seven days.
- Subjects using levonorgestrel IUD can have IUD removed and LevoCept placed on the same day. Insertion can occur on any day of the cycle.

Subjects NOT Using Any Hormonal Birth Control Method (includes copper IUDs)

Subjects NOT using hormonal contraception (including those currently using a copper IUD) must have the IUD inserted in the first 7 days of the menstrual cycle. Removal of a copper IUD and insertion of Levocept may occur on the same day as long as the procedure is performed within the first 7 days of the menstrual cycle.

If pain is present with the subject's current IUD, the subject should not be enrolled.

STATISTICAL METHODS

Effectiveness Outcome

The primary efficacy population will include all subjects aged 18-35 who had a study device successfully placed, provided at least 1 day of e-diary data, and were not pregnant before the IUD was placed.

Effectiveness will be evaluated as the absence of pregnancy during LevoCept use. Pregnancies judged to have occurred during study device use (determined by ultrasound and medical assessments), for which the estimated date of conception was within 7 days after study device removal or calculated date of expulsion, will be included in the per protocol analysis of pregnancies.

The Pearl Index (and 95% confidence intervals) will be calculated for cycles in subjects aged 18-35 at the time of study device placement through the date of LevoCept removal or pregnancy, excluding the following cycles (unless the subject became pregnant in the cycle):

- When back-up contraceptive or emergency contraceptive use was reported by the subject
- When the subject denied having any intercourse.

All pregnancies will be counted in the intent to treat analysis.

Life table analyses will be used as further assessment of pregnancies. Pregnancy rate will also be summarized annually for each of the 3 years and cumulatively.

Safety and Other Outcome Measures

LevoCept ease of placement, placement success, expulsions, and removal success will be descriptively summarized.

Safety evaluations will be based on the incidence of adverse events and serious adverse events and by relationship to the study device or study device placement procedure.

Study device tolerability will be based on changes in bleeding and spotting patterns and study discontinuation (including reasons for discontinuation).

Safety analyses will be based on the experience of all subjects who had attempted study device placement and provided any relevant data. Tolerability analyses will be based on the experience of all subjects who received a study device and provided any relevant data.

Subjects will record frequency and intensity of vaginal bleeding through a daily e-diary. The number of bleeding or spotting days will be summarized for each cycle. In addition, bleeding and spotting will each be summarized separately. Bleeding analyses will include all subjects who had a study device placed and have at least 1 cycle where they were not pregnant and were providing bleeding-related e-diary data on the days in the reference period.

In general, summaries of quantitative variables will include the sample size, mean, median, standard deviation, minimum, and maximum. For qualitative (categorical) variables the summaries will include the number and percentage of subjects in each category.

SAMPLE SIZE

No formal sample size calculations were performed for the study. It is estimated that with 225 subjects enrolled with age 18-35, a 12-month Pearl Index of 0.6 (1 observed pregnancy), and 2,015 evaluable cycles, we will observe a 95% confidence interval for the 12-month Pearl Index of (0.1, 3.3).

2,015 evaluable cycles assumes that in the overall study:

- Each subject will average 10 evaluable cycles of LevoCept use
- 1% of subjects will not provide any e-diary data and will be excluded from the primary efficacy population
- Subjects will not have intercourse or will use backup contraception in 9.2% of cycles

ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
BV	Bacterial Vaginosis
C	Celsius
CBC	Complete Blood Count
CCTN	Contraceptive Clinical Trials Network
CFR	Code of Federal Regulations
cm	Centimeters
CRF	Case report forms
Cu	Copper
CVR	Contraceptive vaginal ring
d	Day
DHHS	Department of Health and Human Services
dL	Deciliter
DSMB	Data Safety Monitoring Board
EC	Emergency contraception
eCRF	Electronic case report form
EDC	Electronic data capture
ECYC	Evaluable for Cycle Control
EE	Efficacy Evaluable
EMR	Electronic medical records
ENDTX	End of treatment
EP	Evaluable for Pregnancy
F	Fahrenheit
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
g	Gram
GCP	Good Clinical Practices
GnRH	Gonadotropin-Releasing Hormone
hCG	Human Chorionic Gonadotropin
HD	Health Decisions
HPV	Human Papillomavirus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-To-Treat
IUD	Intrauterine Device
kg	Kilograms
L	Liter
LTFU	Lost to follow up
MedDRA	Medical dictionary for regulatory activities
MITT	Modified Intent to Treat
mg	Milligrams
mL	Milliliter
mm	Millimeter
NDA	New Drug Application
NIH	National Institutes of Health
N/A	Not Applicable
OC	Oral Contraceptive(s)
Pap Test	Papanicolaou Test
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SAS	Statistical Analysis Software
SCCC	Statistical and Clinical Coordinating Center
SCRN	Screening
SD	Standard Deviation
SOP	Standard Operating Procedure
STD	Sexually Transmitted Diseases
TVUS	Transvaginal ultrasound
UNS	Unscheduled
US	United States
V	Visit
X	Times
WHO	World Health Organization
:	To
/	Per
%	Percent
<	Less than
>	Greater than
≤	Less than or equal to
≥	Greater than or equal to
°	Degrees
±	Plus or minus
+	Plus

1. INTRODUCTION

The LevoCept Intrauterine Contraceptive is designed as a birth control device. There are over 61 million US women in their child-bearing years, ages 15 to 44. Thirty-eight million (38M) use some form of contraception (62%). Thirty-one (31%) percent do not use or need contraception because they are either trying to get pregnant, are pregnant, are infertile or are not sexually active. Seven (7%) percent are at risk for unintended pregnancy since they are using no method[1].

Contraceptive options for those 38 million US women include permanent sterilization (tubal ligation or vasectomy in male partner), contraceptive implants, intrauterine devices, injections, pills, patches, vaginal rings, male and female condoms, other female barrier methods, vaginal spermicides, and behavioral methods such as coitus interruptus and fertility awareness. Of all these methods, oral contraceptives are used by 30% of sexually active women. The more effective methods, such as intrauterine contraceptives, are used by fewer than 10.3% of women and long acting reversible contraception (LARC) 11.6%.[2] The contraceptive CHOICE project showed that the pill failure rate is over 25 times higher than levonorgestrel-releasing contraception.[3,4]

Intrauterine contraceptives have high initial costs, so early discontinuation rates have profound impacts on their cost-effectiveness. The early rates of user dissatisfaction due to complications or side effects may be associated with the materials used in these devices and/or their design. The Copper T380A IUD has been associated with complaints of increased bleeding, inter-menstrual bleeding and cramping pain. The 52mg LNG-IUS (Mirena®) is also associated with early complaints of irregular bleeding patterns, cramping pelvic pain and with amenorrhea.

With high-unintended pregnancy rates in the U.S. (45%)[1], additional effective, safe and long-acting reversible contraceptives are needed. An intrauterine device with levonorgestrel that achieves high contraceptive effectiveness and has improved mechanical advantages could offer an attractive option to women seeking effective protection against unintended pregnancy. We believe the LevoCept Intrauterine Contraceptive embodies these advantages.

2. STUDY DURATION

Subject enrollment will take approximately 5 months. Each subject will be followed for 12 months after device placement for the protocol endpoints, and then every 6 months thereafter for up to 24 additional months for those subjects who wish to continue study device use.

[1]Alan Guttmacher Institute Fact Sheets Oct 2013 (www.guttmacher.org):
https://www.guttmacher.org/fact-sheet/contraceptive-use-united-states#1

[2] Changes in Use of Long-Acting Reversible Contraceptive Methods Among U.S. Women, 2009-2012.
Kavanaugh ML, Jerman J, Finer LB.
Obstet Gynecol. **2015** Nov;126(5):917-27. doi: 10.1097/AOG.0000000000001094.
PMID: 26444110
accessed August 11, 2014.

[3] Secura G, Alllsworth J, Madden T, et al. The Contraceptive CHOICE Project: reducing barriers to long-acting reversible contraception. Am J Obstet Gynecol. 2010:20130;115 e1-7.

[4] Reeves MF, Zhao Q, Secura GM, Peipert JF. Risk of unintended pregnancy based on intended compared to actual contraceptive use. *American Journal of Obstetrics & Gynecology.* 2016.

3. INVESTIGATIONAL PRODUCT DESCRIPTION

The LevoCept Intrauterine Contraceptive is designed for use as a birth control method. The study device consists of a shape memory Nitinol spring with a stem-mounted levonorgestrel-releasing silicone reservoir and small tantalum sleeves at both distal arms for mechanical stability. A monofilament polymer Retrieval Thread is secured at the bottom of the frame.

The study device is shaped such that upon placement in the uterus, the Nitinol spring positions itself at the fundus, with the sleeved arms near the ostia of the fallopian tubes and the levonorgestrel-releasing reservoir in the center of the uterine cavity.

Figure 1 illustrates the basic design and layout of the study device.

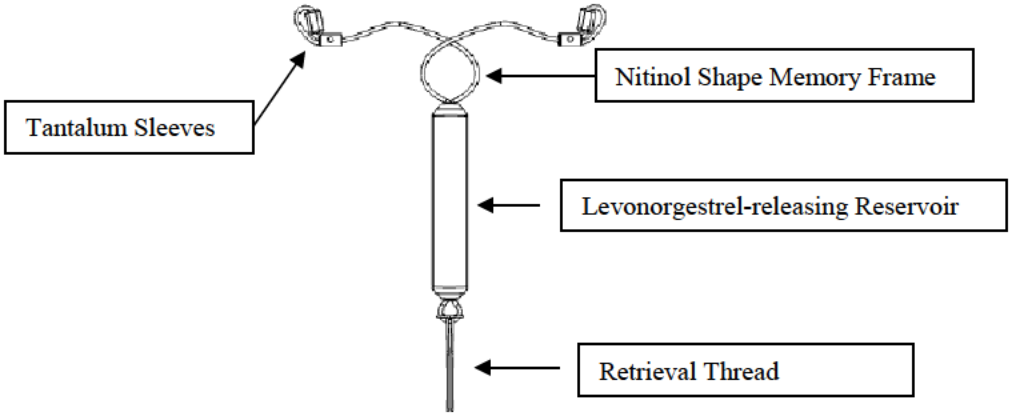

Figure 1 – Design and layout of LevoCept

LevoCept contains 52 mg of Levonorgestrel, which releases at a rate of 20 micrograms per day. The study device is placed using a simple one-step introducer containing the preloaded and sterile study device. It is retrieved with the standard monofilament polypropylene retrieval thread.

Figure 2a shows the study device in its pre-loaded state (directly from the package) in the distal end of the introducer. Figure 2b shows a schematic of the study device oriented in the uterus post placement.

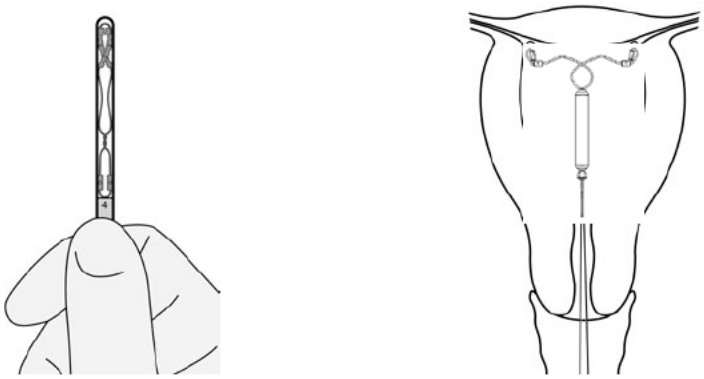

Figure 2 – (a) LevoCept in pre-loaded state (b) orientation in the uterus post placement

4. STUDY TREATMENTS

After the risks and benefits of study participation have been explained to the candidate, her questions have been answered, she has signed a written consent and PHI form, and eligibility has been established, a subject identification number will be assigned by the Study Sponsor or designee. If the subject has a current IUD and pain is present from removal of the IUD, you should wait until the pain has resolved before insertion of LevoCept. If pain is present with the subject's current IUD, the subject should not be enrolled.

4.1 LevoCept Insertion Timing

The following must be followed prior to LevoCept insertion to insure adequate contraception coverage:

4.1.1 Subjects Using Any Hormonal Birth Control Method

Subjects using any hormonal birth control method can have LevoCept placed on any day of the menstrual cycle. If the insertion occurs in the first 7 days of the cycle, the hormonal contraception can be discontinued after insertion. If the insertion occurs after the first 7 days of the menstrual cycle, the subject should continue using hormonal contraception for an additional 7 days.

- Subjects using an implant (Implanon/Nexplanon) who have regular cycles, LevoCept should be inserted within seven days of onset of menses and the implant may be removed the same day.
- Subjects using an implant (Implanon/Nexplanon) who have irregular cycles or amenorrhea, LevoCept should be inserted and the implant should be removed seven days after IUD inserted
- Subjects using an implant (Implanon/Nexplanon) with regular cycles but who are beyond seven days of menses, LevoCept may be inserted but removal of implant should occur after seven days.

- Subjects using levonorgestrel IUD can have IUD removed and LevoCept placed on the same day. Insertion can occur on any day of the cycle.

4.1.2 Subjects NOT Using Any Hormonal Birth Control Method (includes copper IUDs)

Subjects NOT using hormonal contraception (including those currently using a copper IUD) must have the IUD inserted in the first 7 days of the menstrual cycle. Removal of a copper IUD and insertion of Levocept may occur on the same day as long as the procedure is performed within the first 7 days of the menstrual cycle.

4.2 LevoCept Intrauterine Contraceptive (Dosage and Formulation)

LevoCept contains 52 mg of Levonorgestrel which is released at a rate of 20 micrograms per day. A single LevoCept design and dosage will be used in this study. LevoCept will be supplied by ContraMed, LLC. For further details, see the LevoCept Investigator's Brochure.

4.3 LevoCept Supply and Administration

Each LevoCept is preloaded in the inserter and packaged as a single use sterile system. Subjects will have LevoCept placed on "Day 1" of the trial. LevoCept should be stored in its sterile sealed package until study device placement.

See the Investigator's Brochure for a more detailed LevoCept product description, and the LevoCept instructions (e.g. Clinician's Quick Use Guide) for placement and removal instructions.

4.4 LevoCept Storage and Accountability

LevoCept should be stored at 25°C (77°F), with excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Study Device accountability, reconciliation and record maintenance are responsibilities that must be performed by the study site in accordance with all applicable regulatory requirements. Please refer to **Appendix 1,** Investigator Responsibilities for a detailed list of Investigator Responsibilities. All unused Study Devices will be stored for inventory and collection. Shipping procedures to return unused Study Devices are detailed in the Study Reference Manual.

4.5 LevoCept Dosage Modification

All subjects will receive the same LevoCept device and dosage. No Study Devices will be replaced if an expulsion or removal occurs.

4.6 Concomitant Therapy

Concomitant medications are any prescription medications or over-the-counter preparations or routine medications used by the subject taken from the time the subject signs consent shall be documented until Study Exit. Concomitant medications used as prior contraception or used to treat a prior cervical infection within 30 days of screening should also be reported. All concomitant medications, including excluded therapies, must be documented in the Concomitant Medication eCRF.

4.7 LevoCept Retention Compliance

Subjects will be instructed on how to check for study device presence by feeling for the strings in the vagina. Subjects will not be required to routinely check for study device presence, but if a subject believes the study device may have been expelled or is no longer in place, the subject can check for the study device string if desired. If the subject does not feel the strings, feels more than the strings, or has expelled the study device, the subject should be instructed to call for an urgent study visit and refrain from having sex or use appropriate non-hormonal contraception until further evaluation is completed. For detailed instructions regarding management of missing strings, refer to the Study Reference Manual.

5. OBJECTIVES

The scientific objective of this study is to evaluate the effectiveness, study device placement, safety, and tolerability of the LevoCept Intrauterine Contraceptive as birth control in parous and nulliparous women of child-bearing age.

The purpose of the study is to obtain the safety and effectiveness data necessary to support initiation of a longer-term Phase III Pivotal Clinical Study for LevoCept.

5.1 Primary Outcome Measure

The primary outcome measure is effectiveness, evaluated as the absence of pregnancy during LevoCept use. Failure will be calculated using the Pearl Index and by life table analysis. All evaluable cycles prior to discontinuation or planned removal will be included in the primary analysis of effectiveness.

5.2 Safety and Other Outcome Measures

Safety and other outcome measures include:

Study Device Placement:

- Placement success
- Ease of placement

Safety;

- Serious Adverse Events
- Adverse Events

Tolerability:

- Bleeding and spotting patterns
- Discontinuation rate and reasons for discontinuation

6. BENEFITS AND RISKS

6.1 Potential Benefits

No assurances or guarantees can be made regarding the benefits of LevoCept to the study subject. The potential benefits of LevoCept include that it is a hormonal contraceptive method that requires professional placement to be effective.

6.2 Potential Risks / Adverse Reactions

The following adverse events have been reported in association with Mirena[5], the most commonly used levonorgestrel IUD in the US. Serious adverse events and adverse events associated with the Mirena IUD may be relevant because it is also a 52 mg Levonorgestrel-Releasing Intrauterine System Contraceptive. It is not expected that the severity or frequency of any of the following events will be any different with use of the LevoCept. These potential events are listed in alphabetical order, not in order of severity or frequency. See Investigators' Brochure for more information.

- Acne
- Amenorrhea
- Back pain
- Breast cancer
- Breast tenderness
- Depression/depressive mood
- Dysmenorrhea
- Dyspareunia
- Ectopic pregnancy
- Embedment
- Expulsion, partial or complete
- Headache, migraine
- Intrauterine pregnancy
- Irregular menstrual bleeding
- Leukorrhea
- Ovarian cysts
- Pain and cramping
- Pelvic infection
- Perforation
- Sepsis
- Vaginitis
- Vasovagal reaction immediately after placement

There may also be risks that are unanticipated at this time.

6.3 Minimization of Anticipated Risks

Potential risks that may be associated with use of LevoCept have been minimized in this study by the following:

a. Establishing eligibility criteria that exclude subjects who are at higher risk for experiencing an anticipated adverse event;
b. Conducting extensive preclinical and clinical testing prior to the start of this Phase II clinical study;
c. Conducting a risk analysis and incorporating mitigations to eliminate and/or reduce risks to as low as possible in accordance with ISO 14971-Medical Devices – Application of risk analysis to medical devices
d. Selecting investigators with proper level of training and experience in placing IUDs;

[5] Prescribing Information, Mirena, Bayer Healthcare

e. Ensuring adequate monitoring is performed to identify any safety issues associated with the study procedure and subjects;
f. Regularly reviewing reported serious adverse events and adverse events throughout the study and taking appropriate medical measures to resolve the adverse events.

6.4 Safety Review

The Medical Monitor will evaluate safety and pregnancies on an ongoing basis and significant findings will be addressed immediately. A monthly safety and pregnancy review will occur with the Study Principal Investigator to review safety trends, including pregnancies. The medical monitor, the responsible project team and Sponsor personnel will review study drug-related findings periodically and at least bi-monthly. Additional details are located in the Medical Monitoring Plan. If the Medical Monitor identifies any safety issues that may alter the risk benefit ratio of the study product, the Medical Monitor will immediately inform the project team and the Sponsor.

7. SELECTION AND TRAINING OF CLINICAL SITES AND INVESTIGATORS

The study will be conducted at approximately 16 centers in the United States. The primary requirements of selecting an Investigator for this study are: 1) experience and adequate training in a) IUD use and b) conduct of regulated clinical studies, 2) adequate facilities and equipment, 3) adequate patient volume, 4) appropriate personnel and site research staff to support the conduct of the study, and 5) commitment to safety and adherence to the investigational plan.

Prior to acceptance of the site into this study, the Sponsor or its designee will conduct a site qualification visit (if applicable). The site qualification visit will be scheduled to include time with the Principal Investigator, co-investigators, study coordinator, and other study personnel as available. Areas of discussion include a review of personnel training, expertise, and FDA-regulated study experience, this study's specific requirements, and a review of staffing and equipment availability and appropriateness.

Prior to study implementation, the Study Monitor will ensure that study personnel:

- Have appropriate training, facilities, time, and willingness to comply fully with the study requirements.
- A central IRB will be used to review and approve the Investigational Plan wherever possible, but if it is not possible, the investigator will submit this Investigational Plan to the local IRB for appropriate review and obtain written approval for the conduct of the study prior to the initiation of any subject enrollment into this study.
- Maintain all study correspondence, this Investigational Plan, and all related and required records on file at their facility.
- Assume full responsibility for the study investigation at their individual medical practices, clinics, and medical facilities. The Study Monitor will create a written report of the pre-study site visit. Resolution of any concerns and/or completion of any appropriate study activities identified during the pre-study visit will be documented by the Study Monitor, discussed with the Sponsor and submitted to the Investigator.
- Complete any training required by the IRB regarding protection of human subjects.

- Complete training on use of the Case Report Forms (eCRFs) provided by ContraMed representative or designee.
- Review and are familiar with LevoCept instructions (e.g. Clinician's Quick Use Guide, Investigator's Brochure).
- Complete training with LevoCept, provided by a ContraMed representative or designee.

Throughout the conduct of the study, the Sponsor and/or its designees will closely monitor each site for the following:

- Compliance with the investigational plan
- Meeting enrollment commitments
- Accurate and timely submission of CRFs and additional data
- Compliance with ICH E6 Good Clinical Practice (GCP) guidelines
- Compliance with Declaration of Helsinki
- Compliance with IRB and local regulatory requirements

7.1 Laboratories

Local laboratories will be used for any lab tests performed. No central labs will be used in this study.

8. STUDY POPULATION

The study population will be pre-menopausal women, at risk for pregnancy, who are interested in using an intrauterine contraceptive for birth control for at least 12 months. Subjects must provide written informed consent and meet the study entry criteria noted below.

8.1 Inclusion

Subject must meet all of the following criteria to participate in this study:

1. Between 18-40 years of age at the time of study initiation;
   1.1 Enrollment will be targeted for 225 subjects aged 18-35 (for safety and effectiveness analyses) and an additional 25 subjects aged 36-40 (for safety only); (note: all subjects will be included in the analysis for device placement and tolerability);
2. Pre-menopausal, as determined by regular menstrual cycle (28 ± 7 days) for the last 3 months;
   2.1 Based on patient history when not on hormonal contraceptives;
3. Sexually active with a male partner who has not had a vasectomy;
4. Reasonably expect to have coitus at least once monthly during the study period
5. In a mutually monogamous relationship of at least 3-6 months duration
6. Seeking to avoid pregnancy for the next 12 months;
7. Willing to use the study device as the sole form of contraception;
8. Willing to accept a risk of pregnancy;

9. Subjects who are age 21 or older, at time of informed consent, must have a normal PAP or ASC-US with negative high risk HPV test result within the appropriate screen timeframe, and prior to LevoCept insertion;
10. Able and willing to comply with all study tests, procedures, assessment tools and follow-up; and
11. Able and willing to provide and document informed consent and Authorization to Release Protected Health Information (PHI).

8.2 Exclusion

A subject will be excluded from participating in the study if **any** of the following conditions apply:

1. Known or suspected pregnancy; or at risk for pregnancy from unprotected intercourse earlier in current cycle;
2. Subject who anticipates separation from her partner for more than 1 cycle within the next 12 months;
3. A previously inserted IUD that has not been removed by the time LevoCept is placed;
4. History of previous IUD complications, such as perforation, expulsion, infection (pelvic inflammatory disease) or pregnancy with IUD in place.
5. Injection of any hormonal contraceptive (e.g., Depo-Provera) within the last 10 months;
    5.1 Must have had 2 normal menstrual cycles since the last injection;
6. Planned use of any non-contraceptive estrogen, progesterone or testosterone any time during the 12 months of study participation;
7. Postpartum, prior to a minimum of 6 weeks and complete uterine involution;
8. Exclusively breastfeeding before return of menses; Lactating women will be excluded unless they have had at least two normal menstrual periods prior to enrollment.
    8.1 Must have had 2 normal spontaneous menstrual cycles since delivery;
9. Unexplained abnormal uterine bleeding (suspicious for serious condition), before evaluation; Immediately post-septic abortion or puerperal sepsis (must wait a minimum of 3 months);
10. Severely heavy or painful menstrual bleeding;
11. Suspected or known cervical, uterine or ovarian cancer, or unresolved clinically significant abnormal pap smear requiring evaluation or treatment.
12. Any history of gestational trophoblastic disease with or without detectable elevated ß-hCG levels, or related malignant disease without an intervening normal pregnancy;
13. Any congenital or acquired uterine anomaly that may complicate IUD placement, such as:
    13.1 Submucosal uterine leiomyoma
    13.2 Asherman’s syndrome
    13.3 Pedunculated polyps
    13.4 Bicornuate uterus
    13.5 Didelphus or uterine septa
14. Any distortions (e.g. fibroids), in the opinion of the investigator, likely to cause issues during insertion, retention or removal of the IUD;

15. Known anatomical abnormalities of the cervix such as severe cervical stenosis, prior trachelectomy or extensive conization that, in the opinion of the investigator would prevent cervical dilation and study device placement;
16. Current or recent (within the last 3 months) untreated acute cervicitis or vaginitis;
17. Known or suspected breast cancer or other progestin-sensitive cancer now or in the past;
18. Known acute liver disease or liver tumor;
19. Subjects who have an established immunodeficiency;
20. High risk for STDs (e.g., multiple sexual partners);
21. Known or suspected HIV infection or clinical AIDS;
22. Known intolerance or allergy to any component of the LevoCept system; including nickel, silicone or tantalum.
23. Subject had LevoCept placed previously or had 2 attempts at placement;
24. Known or suspected alcohol or drug abuse within 12 months prior to the screening visit;
25. Any general health or behavioral condition that, in the opinion of the Investigator, could represent an increased risk for the subject or would render the subject less likely to provide the needed study information.
26. Subject is currently participating or has participated in another clinical study involving another investigational agent within 30 days of the planned LevoCept insertion date or is planning participation in another clinical trial with an investigational agent within 52 weeks (visit 6) after insertion.

9. INFORMED CONSENT

The person obtaining the informed consent shall:

- Avoid any coercion of or undue influence of the candidate to participate;
- Sustain all the candidate's legal rights;
- Provide complete, detailed description of study events, procedures, follow up and costs/reimbursements using language that is non-technical and understandable to the candidate;
- Ensure that the candidate understands risks and responsibilities;
- Provide ample time for the candidate to consider participation, answer any questions and ensure that satisfactory answers are provided;
- Include dated signatures of the candidate and of the clinical investigator (as applicable);
- Shall ensure that all relevant requirements are met for witness signatures;
- Ensure that the candidate understands the voluntary nature of participation and her ability to withdraw from the study at any time with no adverse impacts on her ability to obtain other services;
- Ensure protection of the candidate’s confidentiality; and
- Provide a copy of the Consent Form signed by the candidate and the person presenting the information for the candidate to take home.

The process that leads to informed consent will be documented.

Each investigational site must provide the Sponsor or designee with a copy of the investigational site's IRB approval letter (or Central IRB letter) and the IRB approved informed consent form, including the Authorization For Release Of Protected Health Information (PHI) form and the Subject Bill of Rights form (California only). The Sponsor or designee must review and approve the IRB approved informed consent form prior to any subject enrollment. The Investigator or designee must review the informed consent form, PHI form and Bill of Rights form (if applicable) with the candidate and explain all study risks and benefits and answer all patient questions before obtaining the candidate's signature on the informed consent form. All subjects must provide written informed consent in accordance with local law and approved by the site's (or Central) IRB.

10. ENROLLMENT

A subject is considered enrolled into the study after signing the informed consent, PHI and Bill of Rights forms (if applicable) and being found eligible based on her history, physical examination, screening tests and LevoCept insertion attempt. If an eligible consented patient withdraws consent before insertion for any reason this would be considered a screen failure. Enrollment is planned at approximately 250 subjects in a five-month period.

11. STUDY SCHEDULE OF ASSESSMENTS

The study schedule of assessments is provided in Table 1.

Table 1. Study Schedule of Assessments

CONTRAMED	Visit 1 - Screening	Visit 2- (LevoCept Placement) Day 1	Visit 3 - Follow up Week 6 ± 1w	Visit 4 – Follow up Week 13 ± 2w	Visit 5 – Follow up Week 26 ± 2w	Visit 6 – Follow up Week 52 ± 2w/	Monthly Contact up to 52 Weeks ±1 w	Exit Visit (Visit 2 – Visit 6/Week 52)	Long Term Follow up Every 6 Months - post 52 Weeks (max 3 yrs. post insertion) ± 2 w	End of each 28-day Cycle Contact (Post 52 Wks ± 1w)	Exit Visit (Post Visit 6/Week 52 – Year 3)
Initiation/Subject Characteristics											
Assessment of Eligibility	X	X									
Distribution of information	X										
Informed consent, PHI and Bill of Rights forms	X										
Demographics and baseline characteristics	X										
Medical/surgical, gynecologic and menstrual history	X										
Safety and Effectiveness											
Vital signs and weight	X	X	X	X	X	X		X	X		X
Height	X										
General physical exam	X					X		X			X
Pelvic exam	X	X	X[1]	X[1]	X[1]	X[1]		X[1]	X[1]		X[1]
Cervical cytology	X[6]										
Cervical infection test (gonorrhea and chlamydia)	X[5,7]										
Transvaginal ultrasound (for verifying study device position)		X	X[2]	X[2]	X[2]	X		X	X[2]		X
Pregnancy test-urine	X	X	X	X	X	X		X[4, 9]	X		X[4, 9]
Prior and interval concurrent medication	X	X	X	X	X	X	X	X	X		X
Adverse events		X	X	X	X	X	X	X	X		X
Other											
IUD placement		X									
IUD placement ease		X									
IUD placement pain		X									
IUD removal ease								X			X
IUD removal pain								X			X
Concomitant contraception		X	X	X	X	X	X	X	X	X	X
Need for contraception	X	X[8]	X[8]	X[8]	X[8]	X[8]	X	X[8]	X[8]	X[8]	X[8]
Patient trained on E-diary	X[3]	X	X	X	X						
E-diary reviewed with subject		X[3]	X	X	X	X	X				
End of study medication								X			X

Note: Screening and enrollment visit *may be combined* if the patient requests and all labs and screening exams are documented as normal.

1. Pelvic exam for LevoCept string check
2. Transvaginal Ultrasound performed at Visit 6 or Exit visit or if indicated
3. First week of e-diary training, prior to LevoCept placement, to be used as training with the subject. This e-diary data is not a part of data collection or analysis. It is intended to ensure the subject understands how to complete the e-diary during the follow up period.
4. Urine pregnancy test will be done 17 days after removal/study exit by the subject at home, with a follow up call by the study coordinator or PI required to document the results.
   Note: If LevoCept is removed before 52±2 weeks, Visit 6 activities should be completed for Exit Visit.
5. Screening for cervical infections is required unless negative results have been obtained within three months of the screening visit.
6. Current with ASCCP cervical cancer screening guidelines. for subjects who will be 21 or older at time of informed consent
7. Insertion can occur without receipt of test results if there is no clinical evidence of infection.
8. If a subject believes the study device may have been expelled or is no longer in place, the subject should call for an urgent study visit and refrain from having sex or use appropriate non-hormonal contraception until further evaluation is completed.
9. For subjects exiting the study due to IUD expulsion: A urine pregnancy test will be done approximately 6-8 weeks after the exit visit by the subject at home, with a follow up call by the study coordinator or PI required to document results

12. STUDY PROCEDURES

12.1 Visit 1: Screening

The following evaluations must be completed prior to the study device placement procedure:

- Subject meets inclusion and exclusion criteria
- Informed Consent, PHI and Bill of Rights forms signed
- Demographics and baseline characteristics
- Medical, surgical, gynecological and menstrual history
- Vital signs (pulse, blood pressure, temperature) and weight
- Height
- General physical exam
  - General Appearance
  - Skin
  - HEENT
  - Thyroid
  - Lungs
  - Back
  - Breasts
  - Heart
  - Abdomen
  - Extremities
  - Neurological
- Pelvic exam
- Cervical cytology (current with ASCCP cervical cancer screening guidelines), for subjects who will be 21 or older at time of informed consent. A normal PAP or ASC-US with negative high-risk HPV test results must be received within the appropriate screen timeframe, and prior to LevoCept insertion.
- Cervical infection tests (gonorrhea and chlamydia), unless negative results

have been obtained within three months of the screening visit. Insertion can occur without receipt of test results if there is no clinical evidence of infection

- Urine pregnancy test
- Prior and concurrent medications
- Need for contraception (review and discuss the subject's need for appropriate contraception during the screening period)

Subjects will be trained on e-diary use and completion. E-diary instructions will be dispensed to the subject at this visit. If the subject will be using a mobile device (e.g. cellphone or tablet) to complete the e-diaries, subject e-diary accessibility should be confirmed. E-Diary data from screening to the day of LevoCept placement is intended for training purposes and will not be included in the data analysis.

12.2 Visit 2: LevoCept Placement (Day 1)

See Section 4.1 for LevoCept insertion timing instructions. Subjects must have a negative urine pregnancy test just prior to LevoCept placement. Initiation of the LevoCept is consistent with standard IUD placement. Refer to the Clinician's Quick Use Guide and Investigator's Brochure for specific instructions.

If placement is unsuccessful, a second attempt may be made on the same day or within one (1) week following the first attempt. If a second attempt is also unsuccessful, the subject will be discontinued early from the study. The need for cervical dilation to facilitate placement of LevoCept will be left to the discretion of the investigator and subject; however, it is recommended that placement be tried first without prior cervical dilation. Use of cervical dilation will be recorded on the case report form. The need for pain control will also be left to the discretion of the investigator and subject. Any medications given for pain control will be recorded on the Concomitant Medications case report form.

Prior to LevoCept placement, the following evaluations will be completed:

- Entry criteria confirmed
- Vital signs and weight
- Pelvic Exam
- Pregnancy test, urine
- Prior and concurrent medications
- Any adverse events.

Following LevoCept placement, the following will be performed:

- LevoCept placement ease
- LevoCept placement pain
- LevoCept position (evaluated by Transvaginal Ultrasound)
- Concomitant contraception
- Need for contraception if LevoCept was not properly placed (If a subject believes the study device may have been expelled or is no longer in place, the subject should call for an urgent study visit and refrain from having sex or use appropriate non-hormonal contraception until further evaluation is completed. (See Section 4.7 for details)

- Review the completed practice diaries and discuss with the subject any further training that is required and answer any questions the subject may have about how to correctly complete the diaries.
- Instruct the subject to contact the site immediately if she thinks she has become pregnant.

12.3 Visits 3-6 Follow-up (Week 6±1w,13±2w, 26±2w and 52±2w/)

The subject will return for follow up visits at preplanned intervals following placement of the LevoCept. At these follow up visits, the following will be performed:

- Vital signs and weight
- Pelvic exam (string check)
- Pregnancy test, urine
- Transvaginal ultrasound (if indicated)
- Concomitant contraception
- Need for contraception (If a subject believes the study device may have been expelled or is no longer in place, the subject should call for an urgent study visit and refrain from having sex or use appropriate non-hormonal contraception until further evaluation is completed. (See Section 4.7 for details)
- Interval and concurrent medications
- Adverse events
- E-diary review with subject
- Verify sexual activity and any back-up method is documented
- Instruct the subject to contact the site immediately if she thinks she has become pregnant.

Additionally, at the Visit 6/Week 52 visit, the following will also be performed:

- Transvaginal ultrasound to document LevoCept position
- General physical exam

12.3.1 Exit Visit (Visit 2 – Visit 6/Week 52)

In addition to the assessments in Section 12.3, the following will be performed for subject's exiting the study between Visit 2 – Visit 6/Week 52:

- Transvaginal ultrasound to document LevoCept position
- General physical exam
- Prior to removal of LevoCept, it should be determined if the subject has had vaginal intercourse (with intravaginal ejaculation) within the last 72 hours. If confirmed, LevoCept removal and the Exit visit should be rescheduled. The subject should be instructed to avoid vaginal intercourse for 72 hours or more before LevoCept removal. If rescheduling is not possible, the subject should be instructed not to have intercourse within 72 hours of LevoCept removal due to risk of pregnancy. The subject's preferred method of contraception will be provided at the Exit visit.
    - If the subject elects a non-hormonal method of contraception, a 14-day supply will be provided by the site.

  - If the subject elects to use hormonal contraceptive pills as the preferred method of contraception, a one month supply of hormonal contraceptive pills will be provided to the subject by the site as a contraceptive option for the first two weeks following LevoCept removal.
  - The subject will also be provided with condoms to take with her as an extra precaution if the subject fails to acquire the contraception noted above.
  - In addition to the above, subjects who desire to have LevoCept removed immediately and have had vaginal intercourse (with intravaginal ejaculation) within 72 hours should also be provided with emergency contraception (e.g. ella®, Plan B One-Step®)
- Subject should be reminded to avoid conception within 7 days after LevoCept removal.
- LevoCept Removal
  - LevoCept removal ease
  - LevoCept removal pain
- Urine pregnancy test will be done 17 days after removal/study exit by the subject at home, with a follow up call by the study coordinator or PI required to document results.

12.3.2 Subjects Exiting the Study Due to IUD Expulsion:

In addition to Sections 12.3 and 12.3.1, when a subject is exiting the study due to an IUD expulsion, the following will be performed:

- A urine pregnancy test will be done approximately 6-8 weeks after the exit visit by the subject at home, with a follow up call by the study coordinator or PI required to document results.

12.3.3 Monthly Contact (Up to 52 Weeks ± 1 w)

Subjects will be contacted each month from the time of IUD insertion, to confirm completion of the monthly e-diary for:

- The need for additional contraception (If a subject believes the study device may have been expelled or is no longer in place, the subject should call for an urgent study visit and refrain from having sex or use appropriate non-hormonal contraception until further evaluation is completed. (See Section 4.7 for details);
- Use of emergency contraception;
- Documentation of menstrual and intermenstrual bleeding;
- Documentation of menstrual pain or cramping

Additionally, the following will occur during the monthly contacts:

- Assess if there have been any adverse events since the last contact;
- Use of concomitant medications;
- Collection of any missing diary information (frequency of intercourse, pain with intercourse and use of concomitant or emergency contraception); and
- Resolution of any prior serious adverse events or adverse events.

12.4 Long-term Follow-up, post 52-weeks visit (Every 6 Months: Months 18-30 (±4wks) and 3 yrs (-3wks/+4wks)

At 52 weeks, subjects will be allowed to continue with the study device with a follow-up office visit every 6 months for a maximum of three years post study device placement. During these visits, the following will be performed:

- Vital signs and weight
- Pelvic exam (string check)
- Transvaginal ultrasound If unable to confirm IUD placement by string check or if indicated
- Pregnancy test, urine
- Interval and concurrent medications
- Adverse events
- Concomitant contraception
- Need for contraception (If a subject believes the study device may have been expelled or is no longer in place, the subject should call for an urgent study visit and refrain from having sex or use appropriate non-hormonal contraception until further evaluation is completed. (See Section 4.7 for details)
- Verify sexual activity and any back-up method is documented
- Instruct the subject to contact the site immediately if she thinks she has become pregnant.

12.4.1 End of Each 28-day Cycle Contact (Post 52 Weeks + 1 w)

Subjects will be contacted (e.g. phone calls, e-mail or text message) at the end of each 28-day cycle, beginning after the 52-week visit. Cycles are determined from the day of LevoCept insertion:

- Verify sexual activity
- Document any back-up contraception methods

12.4.2 Exit Visit (Post Visit 6/Week 52 – Year 3)

In addition to the assessments in Section 12.4, the following will be performed for subject's exiting the study between Visit 6/Week 52 and year 3:

- Transvaginal ultrasound to document LevoCept position
- General physical exam
- Prior to removal of LevoCept, it should be determined if the subject has had vaginal intercourse (with intravaginal ejaculation) within the last 72 hours. If confirmed, LevoCept removal and the Exit visit should be rescheduled. The subject should be instructed to avoid vaginal intercourse for 72 hours or more before LevoCept removal. If rescheduling is not possible, the subject should be instructed not to have intercourse within 72 hours of LevoCept removal due to risk of pregnancy. The subject's preferred method of contraception will be provided at the Exit visit.
    - If the subject elects a non-hormonal method of contraception, a 14-day supply will be provided by the site.
    - If the subject elects to use hormonal contraceptive pills as the preferred method of contraception, a one month supply of

hormonal contraceptive pills will be provided to the subject by the site as a contraceptive option for the first two weeks following LevoCept removal.
    - The subject will also be provided with condoms to take with her as an extra precaution if the subject fails to acquire the contraception noted above.
    - In addition to the above, subjects who desire to have LevoCept removed immediately and have had vaginal intercourse (with intravaginal ejaculation) within 72 hours should also be provided with emergency contraception (e.g. ella®, Plan B One-Step®)
- Subject should be reminded to avoid conception within 7 days after LevoCept removal.
- LevoCept Removal
    - LevoCept removal ease
    - LevoCept removal pain
- Urine pregnancy test will be done 17 days after removal/study exit by the subject at home, with a follow up call by the study coordinator or PI required to document results.

12.4.2 Subjects Exiting the Study Due to IUD Expulsion:

In addition to Sections 12.4 and 12.4.1, when a subject is exiting the study due to an IUD expulsion, the following will be performed:

- A urine pregnancy test will be done approximately 6-8 weeks after the exit visit by the subject at home, with a follow up call by the study coordinator or PI required to document results.

12.5 Early Discontinuation Visit

If a subject requests LevoCept removal because of an adverse event, the Study Exit Visit described in Section 12.3 above should be completed and documented on the CRF at the time of LevoCept removal. The subject will be followed until resolution of the event or 30 days after removal, whichever occurs first. Subjects experiencing an ongoing adverse event will continue to receive the appropriate follow-up medical care.

If a subject requests early discontinuation and LevoCept removal to become pregnant, the Study Exit Visit should be completed and documented on the CRF at the time of LevoCept removal. Additionally, subjects shall be followed for either; six (6) months, until they decide to no longer try to conceive or they become pregnant, whichever comes first. Outcome data regarding subject's ability to conceive, or the decision to no longer try to become pregnant will be collected via subject contact and documented.

12.6 Unscheduled Visits

Unscheduled visits must be documented on an unscheduled visit CRF. Medical evaluations will be conducted as indicated by the reason for the unscheduled visit.

12.7 Emergency Contraception

If the subject suspects the LevoCept has expelled, she should contact the study site immediately. The subject should be counselled to avoid intercourse until an exam can confirm expulsion. Emergency contraception may be administered, according to product labelling, if the subject suspects expulsion has occurred and an act of intercourse might be unprotected, and she does not want the risk of pregnancy. If the subject is subsequently found to have an *in-situ* IUD and desires to continue in the study, the cycle during which she used EC will not be included in the analysis unless the subject conceives. If the IUD is expelled, she will be exited from the study and followed for 6-8 weeks for occurrence of pregnancy.

12.8 Lost to Follow-up

A subject should not be considered "lost to follow-up" until the site has made at least three contact attempts (e.g. phone calls, e-mail or text message) and a certified letter is sent. The date of the certified letter or last attempted contact by the site is the subject's exit date, whichever is later. The End of Trial and any Adverse Event or Concomitant Medication eCRFs should be submitted within a week of the subject's lost to follow-up date. The site should continue attempts to contact the subject monthly for an additional 3 months to bring the subject back to remove the LevoCept IUD.

If after a subject is determined to be lost to follow-up and subsequently becomes available again, and the Principal Investigator determines she is a fit study subject, she can re-join the study.

13. Diaries

Subjects will be instructed to complete diaries daily. Diaries are designed to collect the following information for each day of the 28-day cycle:

- Day of cycle
- Absence or presence of menstrual or other bleeding (none, spotting, normal or heavy)
- LevoCept expulsion (yes, no, suspected)
- Usage of additional birth control methods and type of birth control used
- Presence of menstrual pain or cramping
- Frequency of intercourse
- Pain with intercourse

14. CONCOMITANT MEDICATIONS

Concomitant medications include any medication or health product (any prescription medications or over-the-counter preparations) taken from the time the subject signs the informed consent documents until Study Exit. Concomitant medications used as prior contraception or used to treat a prior cervical infection within 30 days of screening should also be reported. All concomitant medications, including excluded therapies, must be recorded appropriately on the eCRF.

15. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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 must

report all SAEs to the Study Sponsor, whether or not they result from study participation, within 24 hours of learning of the event.

15.1 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 meaning that the patient was at immediate risk of death from the event at the time that the event occurred. It does not include an event, which hypothetically might have caused death if it occurred in a more severe form.
- 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 device; or
- 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 serious adverse events include, but are not limited to: intensive treatment in an emergency room, hospitalization for any reason, and extensive treatment at home for an adverse event. An ectopic pregnancy is considered a serious adverse event.

15.2 Definition of An Adverse Event

An **adverse event** is any untoward medical occurrence in a clinical investigation subject administered an investigational 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 date before the first date of attempted study device placement is usually considered to be pre-existing, and should not be documented in the eCRF as an AE, unless there is an increase in frequency or intensity of that 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 first attempt of study device placement through Study Exit should be recorded as an AE on the eCRF. All AEs must be recorded on the AE eCRF regardless of the severity or relationship to study device. It is important that Investigators also report all AEs that result in expulsion or removal of the investigational product being studied, whether serious or non-serious.

Pregnancy is an outcome, and not an adverse event in this study.

15.3 Causality: Serious Adverse Event and Adverse Event Relationship to Study Treatment

The Investigator will assess the relationship of the SAE and AE to study device placement procedure (procedure) or study device by using the following general guidelines:

Not Related: A causal relationship between the study device 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 laboratory test abnormality, with a temporal relationship to procedure or study device initiation which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Probably Related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to first attempt of study device placement, 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 laboratory test abnormality, with a reasonable time sequence to first attempt of study device placement, cannot be attributed to concurrent disease or other medical devices, drugs, or chemicals, and which follows a clinically reasonable response on withdrawal.

15.3.1 Clarification of Adverse Events Related to Study Procedures

Any untoward event that occurs from the beginning of the study device placement procedure until completion of placement, or from the beginning of the removal procedure until the completion of removal, will be reported as an AE. The AE should be recorded on the AE eCRF with a causality assessment of “related to study device placement procedure.” If the AE also meets the criteria for an SAE, an SAE eCRF should be completed and submitted to Sponsor.

15.4 Serious Adverse Event and 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 usual daily activity and typically requires systemic drug therapy or other treatment (a severe AE may not necessarily qualify as an 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.
- Fatal: An AE that was the cause of the subject’s death

15.5 Adverse Event Outcome

The Investigator will categorize the outcome of each SAE and AE according to the definitions below:

- **Resolved**: The subject recovered from the SAE or 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 SAEs and AEs are not considered resolved as a result of death and no SAE or 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. Note: 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.

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 or SAE eCRF. If no diagnosis is known and clinical signs or symptoms are not present, then the abnormal finding should be recorded on the AE or SAE eCRF. If an SAE report is completed, pertinent laboratory data should be recorded on the SAE eCRF, preferably with baseline values and copies of laboratory reports.

15.6 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** if the Investigator determines that an adverse event meets the protocol definition of an SAE.

All SAEs occurring from the time of LevoCept insertion through study exit require immediate 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;
- Submit the completed form to Sponsor;
- For fatal or life-threatening events, also submit 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 Sponsor;
- The SAE eCRF should be completed as thoroughly as possible and signed by the Investigator before transmittal to Sponsor. It is very important that the Investigator provides an assessment of the causal relationship between the event and the study device at the time of the initial report; and
- 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.

15.7 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 study device placement or that are present at baseline and worsen following the placement of LevoCept are included as AEs (or 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.

15.8 Documenting Adverse Events

Any AE occurring from the beginning of the study device placement procedure through Study Exit must be documented in the subject's study records and on the AE eCRF. SAEs that occur during the study must be documented in the subject's study record, on the AE eCRF and on the SAE eCRF as appropriate.

The investigator's assessment of causality, severity and status of the adverse event must be documented. 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 Sponsor performs a cumulative analysis of similar events.

15.9 Follow-up of Adverse Events and Serious Adverse Events

All AEs and SAEs must be followed until resolution, the condition stabilizes, 30 days post study device removal, or the subject dies or is lost to follow-up (including withdrawal of consent), whichever occurs first. 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.

15.10 Clarification in Reporting of Deaths

All subject deaths (regardless of relationship to study device) should be reported that occur from the beginning of study device placement through Study Exit. The information should be recorded on the Subject Death form and the SAE eCRF.

15.11 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 device placement through Study Exit require reporting to the Sponsor. In addition, if the Investigator learns of any SAE at any time after a subject has had the study device removed, and such event seems reasonably related to study drug, the Investigator should immediately notify the Sponsor.

15.12 Study Device Malfunction

Should the study device not perform mechanically as expected, it is essential that it be returned to the study Sponsor for assessment.

16. PROTOCOL VIOLATIONS and DEVIATIONS

Except in the event of a medical emergency or where it is necessary to protect the safety, rights or welfare of the study subject, any changes to the protocol will require written approval of ContraMed LLC or designee. Violations or deviations from the Clinical Investigational Plan to protect the health and safety of the subject will be reported to the IRB and as required by local regulations. All protocol violations or deviations will be recorded, tracked and reviewed periodically by ContraMed and its designee, according to process established prior to first patient enrolled. A protocol violation or deviation may be requested in advance of implementation and will be reviewed for approval by ContraMed or its designee, or a violations/deviation may be identified after the fact, by the Investigator, ContraMed, or the monitoring staff. Investigators will be asked to provide an explanation for the all violations and deviations identified. ContraMed, or designee, will be responsible for analyzing deviations and may implement corrective actions as necessary.

17. SUBJECT CONFIDENTIALITY

At all times throughout this study, all parties shall strictly observe the confidentiality of subject's health information. All data shall be secured against unauthorized access. Each subject participating in this study will have consented to allow access to her data, as described during the informed consent process and documented in the signed informed consent form. Each subject will also sign an Authorization For Release of Protected Health Information (PHI) form granting ContraMed and its designees access to her medical records, should she receive medical care from non-study sites where she gets care (e.g., emergency room, urgent care, etc.).Each subject will be assigned a unique identifier. All eCRFs will be tracked, evaluated, and stored using only this unique identifier. HIPAA guidelines and regulations will be followed.

The Investigator will maintain a confidential study subject list identifying all enrolled subjects. This list will contain the assigned study subject's unique identifier and name. The Investigator bears responsibility for keeping this list confidential. This list will not be provided to the study Sponsor and is only to be used at the study center.

Monitors and auditors will have access to the study subject list and other personally identifying information of study subjects to ensure that data reported in the eCRFs corresponds to the person who signed the consent form and the information contained in the original source documents. Such personal identifying information may include, but not limited to, the subject's name, address, date of birth, gender, race and medical record number.

In an effort to protect subject confidentiality, any source documents copied for monitoring purposes by the Sponsor or designee will be identified using the subject's assigned unique identifier and personal identifying data will be obscured.

18. PREGNANCY DETERMINATION AND FOLLOW UP

Suspected pregnancy will be confirmed with a urine pregnancy test. A positive urine test will be confirmed by a serum test and/or ultrasound as is appropriate. Pregnancies will be promptly confirmed and dated by ultrasound evaluation and medical assessment as needed. Presence or absence of the study device will also be determined by ultrasound. Removal of the study device, if in place, will be performed as deemed appropriate by the study physician and upon obtaining subject consent (note: removal itself may be performed by another clinician, such as a nurse practitioner). Consideration of study device removal should include the following standard of care criteria: If the subject has an intrauterine pregnancy in the first trimester and the study device is seen to be in the uterine cavity or cervix on ultrasound, remove the study device if the retrieval threads are visible. If the retrieval threads are not accessible, the IUD should remain in the uterus until delivery (abortion or term).

Subjects will be counseled and followed through completion of pregnancy, and the clinical outcome will be recorded.

19. DATA MONITORING AND QUALITY CONTROL

19.1 Monitoring of Clinical Sites and Investigators

Periodic monitoring visits will be made at the investigational site throughout the clinical study to ensure that the Investigator obligations are fulfilled and all applicable regulations and guidelines are being followed. These visits will ensure that the facilities remain acceptable, the investigational plan is being followed, the IRB and local authorities have been notified of approved investigational plan changes as required, complete records are being maintained, appropriate and timely reports have been made to the Sponsor and/or its designees and the IRB, study device and study device inventory are controlled and the Investigator is carrying out all agreed upon activities. The Sponsor will reserve the right to remove either the Investigator or the investigational site from the study for noncompliance with the investigational plan or regulations. See monitoring plan for full details.

19.2 Electronic Case Report Forms (eCRF)

Electronic case report forms (eCRFs) will be used to collect all subject data during the study

The Investigator is responsible for the accuracy and completeness of all data on the eCRFs.

Sponsor personnel or designee will review completed eCRFs at regular intervals throughout the study. Information on the eCRFs will be compared to information originally recorded on source documents related to the study. Information on the eCRF must match the same information on the source documents or a data query will be issued.

The Sponsor will use the study data for statistical and tracking purposes and will treat the information as confidential.

19.3 Data Collection and Management

Qualified study staff at the investigational site will perform primary data collection. The Sponsor monitors and/or designees will perform clinical study monitoring of 100% of the subjects who pass screening evaluations and undergo LevoCept placement. This monitoring will include review of eCRF data with verification to the source documentation.

All eCRFs will be reviewed for completeness, validity, and consistency. Queries will be generated and resolved with the sites and all protocol deviations will be recorded on the eCRF.

19.4 Maintaining Records

The Sponsor and/or its designees will maintain copies of correspondence, data, shipment of study devices, adverse study device effects and other records related to the clinical study. The Sponsor will maintain records related to the signed Investigator agreements.

19.5 Record Retention

All study records and reports will remain on file for a minimum of two years (or longer if local law or clinic administration requires) after the latter of the following two dates: 2 years after a marketing application is approved, or if an application is not approved, until 2 years after shipment and delivery of the study device for investigational use is discontinued and FDA has been so notified. Study records should only be discarded upon written notification from the Sponsor. All records and reports are subject to inspection at any time.

19.6 Investigational Product Accountability

The Sponsor or designee shall ship investigational study devices only to qualified investigators. The Investigator shall maintain adequate records of the receipt and disposition of all investigational study devices. The Investigator shall return any unused devices, opened or unopened, to the Sponsor or its designees when the study has completed.

19.7 Study Closeout

Upon completion of the clinical study (when all subjects enrolled have completed the last required visit and the eCRFs and queries have been completed), the Sponsor and/or its designees will notify all investigational sites of closeout. Unused study devices, and any unused study materials will be collected and returned to the Sponsor and/or its designees.

19.8 Audits and Inspections

The Investigator will permit access to original medical records and provide all requested information in the event that the Sponsor and/or its designees or national regulatory authorities initiate any audits or inspections. In the case that it is a non-Sponsor initiated audit, the investigator must contact the Sponsor as soon as possible after notification of intent to audit.

19.9 Annual, Interim and Final Report

Annual, interim and final reports will be completed in accordance with the applicable local and federal regulations. A final report will be completed even if the study is prematurely terminated.

20. STATISTICAL METHODOLOGY AND ANALYSIS

A detailed statistical analysis plan will be finalized prior to locking the database to conduct the statistical analysis in accordance with the methods presented below.

20.1 Analysis Populations

The following analysis populations will be created:

All Enrolled: All subjects enrolled into the study.

Intent to Treat (ITT) / Safety: All enrolled subjects who underwent the study device placement procedure, regardless of whether the study device was successfully placed or not.

Evaluable for Pregnancy (EP):
Subjects must meet requirements 1 and 2 to be EP. Subjects must also meet either requirement 3 **or** requirement 4 to be EP.

1. between 18 to 35 years of age (inclusive) at enrollment
2. at least one report of pregnancy status after being enrolled
   AND
3. have at least 1 cycle of e-diary with intercourse and without any backup contraception or emergency contraception (EC)
   OR
4. became pregnant while LevoCept was in place.

Evaluable for Cycle Control (ECYC): all subjects Evaluable for Pregnancy with at least one cycle for which: A) a pregnancy did not occur; and B) there is bleeding related e-diary data.

20.2 Disposition of Subjects

The number of subjects who are enrolled, complete scheduled study visits and who complete the study will be summarized for the All Enrolled population.

20.3 Demographic and Other Subject Characteristics

Subject demographics and pre-treatment characteristics will be summarized for the All Enrolled Population.

20.4 Extent of Exposure

Exposure (number of subjects with LevoCept placed and number of cycles of use) to the study device will be summarized.

20.5 Pre-Trial and Concomitant Medications

Concomitant medications include any medication or health product (any prescription medications or over-the-counter preparations) taken during the study. Pre-trial medications include any contraception or medication used to treat a prior cervical infection taken within 30 days of screening. The number and percentage of subjects using medications, as captured on the Concomitant Medication eCRF, will be tabulated according to the medication's World Health Organization Anatomical Therapeutic Drug Class and Generic Term. Pre-trial and concomitant medications will be presented separately.

20.6 Primary Outcome

The primary outcome measure is effectiveness and will be evaluated as absence of pregnancy during LevoCept use. Pregnancies judged to have occurred while a study device was in place (determined by ultrasound and medical assessments) will be included in the analysis of pregnancies.

For the primary evaluation of effectiveness, the Pearl index (and 95% confidence intervals) will be calculated in subjects aged 18-35 at the time of LevoCept placement through the date of LevoCept removal or pregnancy, excluding the following (unless the subject became pregnant in the cycle):

- Cycles where back-up contraception use was reported by the patient
- Cycles with no intercourse.
- Cycles in which emergency contraception was used

The Pearl Index is based on 28-day cycles and defined as the number of pregnancies per 100 woman-years (with one year comprising 13 28-day cycles). The cycle is defined as 28 days with the day of LevoCept placement as cycle 1

day 1. Pearl index will be summarized annually for each of the 3 years and cumulatively.

The EP population will be used for the primary evaluation of effectiveness.

Life table (Kaplan-Meier method) analyses will be used as further assessment of pregnancies. Pregnancy rate will also be summarized annually for each of the 3 years and cumulatively.

20.7 Safety and Other Outcome Measures

All safety and other outcome measures will be analyzed using the ITT/Safety Population unless noted otherwise. Confidence intervals will be provided to support interpretation of the observed safety rates.

LevoCept Characteristics
Study device ease of placement and placement success will be summarized. Cumulative study device expulsion rates will be summarized

Adverse Events
The number and percentage of subjects with each adverse event and serious adverse event will be presented in a table by MedDRA system-organ class and preferred term. Summaries will also be presented by relationship to the LevoCept placement 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 intrauterine contraceptive, including:

- Acne
- Amenorrhea
- Back pain
- Breast cancer
- Breast tenderness
- Depression/depressive mood
- Dysmenorrhea
- Dyspareunia
- Ectopic pregnancy
- Embedment
- Expulsion, partial or complete
- Headache, migraine
- Intrauterine pregnancy
- Irregular menstrual bleeding
- Leukorrhea
- Ovarian cysts
- Pain and cramping
- Pelvic infection
- Perforation
- Sepsis
- Vaginitis
- Vasovagal reaction immediately after placement

LevoCept Safety-Related Removal Rates and Expulsion Rates

Cumulative LevoCept safety-related removal rates and expulsion rates at each year will be summarized.

Bleeding and Spotting Patterns
Vaginal bleeding and spotting will be recorded daily by the subject in her e-diary. The ITT and ECYC populations will be used for the bleeding and spotting summaries. The number of bleeding or spotting days will be summarized for each cycle. In addition, bleeding and spotting will be summarized separately. Subjects who discontinue the study due to bleeding complaints prior to completing one 28-day cycle will be included in the bleeding analysis.

Occurrence and Severity of Dyspareunia
Pain with intercourse will be recorded daily by the subject in her e-diary. The occurrence and severity of dyspareunia will be summarized for each cycle in ECYC population.

Other Safety Assessments
Changes in vital signs from baseline to each visit will be summarized for the physical examination and vital sign results.

20.8 Monitoring of Safety and Pregnancy

Periodic reviews of safety and pregnancy rates will be conducted by a Medical Monitor. New findings of safety concerns or pregnancies will be communicated to all study sites. A Clinical Events Committee (CEC) will be assembled to review study data if >1 pregnancy is reported.

APPENDIX 1. INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for ensuring that the clinical study is conducted according to the Investigator Agreement, Clinical Investigational Plan (CIP), all conditions of national regulatory requirements, the governing IRB, and in accordance with the highest standards of medical and ICH E6 Good Clinical Practice (GCP), and the Declaration of Helsinki.

The Investigator(s) shall be responsible for the day-to-day conduct of the investigation as well as for the safety and well-being of the human subjects involved in the clinical investigation. The Investigator(s) shall:

a) Have the resources to conduct the investigation properly

b) Ensure that conducting the investigation will not give rise to a conflict of interest

c) Obtain from the Sponsor the information which the Investigator(s) judges essential about the study device and be familiar with this information

d) Be well acquainted with the protocol before signing it

e) Support the monitor and/or auditor, if applicable, in their activities to verify compliance with the protocol, to perform source data verification and to correct the eCRFs where inconsistencies or missing values are identified

f) Discuss with the Sponsor management any question or modification of the protocol

g) Make sure that the protocol is followed by all responsible for the conduct of the study at his/her institution. Any deviation shall be documented and reported to the study Sponsor.

h) Make the necessary arrangements to ensure the proper conduct and completion of the investigation

i) Make the necessary arrangements for emergency treatment, as needed, to protect the health and welfare of the subject

j) Ensure that appropriate IRB approvals are obtained prior to the start of the investigation

k) Provide the communication from the IRB to the study sponsor

l) Inform the IRB about any serious adverse device effects in accordance with the IRB requirements.

m) Inform the Sponsor about any adverse events and adverse device effects in a timely manner and in accordance with the timelines laid out in this protocol

n) Endeavor to ensure an adequate recruitment of subjects

o) Ensure that the subject has adequate time and information to give informed consent

p) Ensure that informed consent authorization to release protected health information is obtained and documented prior to any study specific evaluations or procedures being performed

q) Ensure that clinical records are clearly marked to indicate that the subject is enrolled in this study

r) Provide subjects with well-defined procedures for any emergency situation and safeguard the subject's interest

s) Ensure that information which becomes available as a result of the clinical investigation which may be of importance to the health of a subject and the continuation of the investigation shall be made known to: 1) the Sponsor; 2) the subject; and 3) the subject's personal clinician (with the subject's approval), if pertinent to the safety or well-being of the subject

t) Inform the subject and/or the subject's physician (with the subject's approval) about any premature termination or suspension of the investigation with a rationale for study termination

u) Have primary responsibility for the accuracy, legibility and security of all investigational data, documents and subject records both during and after the investigation

v) Review and sign each subject's eCRFs (last page only)

w) Be responsible for the supervision and assignment of duties at his/her study center

x) Ensure that all investigational devices are accounted for (number of devices used, discarded and returned to the Sponsor)

y) Disclose to the Sponsor sufficient accurate financial information to allow the Investigator to submit complete and accurate certification or disclosure statements, and update the information during the course of the investigation and for one year following the completion of the study

z) Ensure that the Investigator discloses to the Sponsor if the Investigator has ever been associated with terminated research and the reason for such termination is provided

aa) Ensure that the Investigator discloses to the Sponsor if the Investigator has ever been barred from conducting or participating in clinical research.

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