NCT03633799

STUDY PROTOCOL

A Phase 3, Prospective, Multi-Center, Single-Arm, Open-Label Study to Evaluate VeraCept®, a Long-Acting Reversible Intrauterine Contraceptive for Contraceptive Efficacy, Safety, and Tolerability

DOCUMENT DATE: 30 Jun 2023

Review & Approval:

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Clinical Investigation Plan CMDOC–0042 Version 7.0 / 30 June 2023, Attached 67 pages

DOCUMENT REVISION HISTORY

Rev.	Description	Originator	Effective Date
A	Initial Protocol	MJ Schreifels	08.12.17
B	Revisions based on FDA feedback	MJ Schreifels	11.01.17
C	Remove randomized arm	MJ Schreifels	06.15.18
D	Addresses questions and comments made during the Investigator Meeting and during subject enrollment to-date	MJ Schreifels	03.22.19
E from Protocol 4A	This version is only applicable to the sites participating in the CMDOC-0045 study. To allow subjects who were previously enrolled into the CMDOC-0045 study, and who were randomized into the ParaGard® arm, to be eligible for this CMDOC-0042 study.	MJ Schreifels	04.04.19
F	Clarify exclusion criteria, clarify double barrier method, add menstrual cup use information, and update AE outcome definition	MJ Schreifels	06.17.19
G	Added Pandemic Response section. Added menstrual product use collection to study procedures. Added Pre-Removal Planning guidelines (Appendix 4) and VeraCept Removal Instructions (Appendix 5). Updated potential risk section. Changed "IUD" to "IUS" as appropriate. Changed "Introducer" to "Inserter" throughout. Provided administrative changes and clarifications. Updated Phase 2 study results. Combined Protocol Versions 4A and 5A into Version 6 (added exclusion #21a).	E Lopez	06.30.21

Rev.	Description	Originator	Effective Date
H	Updated Sebela Pharmaceuticals, Inc. to Sebela Women's Health. Extended study duration to 8 years. Added additional study visits and analyses. Updated secondary endpoints and sample size. Added clarification for excluding subjects from the EP population. Updated potential risk section. Added a Subject Satisfaction Survey for subjects exiting study for years 6-8. Updated requirements for missed visits and discontinuing subjects as lost to follow-up. Updated timelines for collection of adverse events and concomitant medications. Added the need to follow any off-treatment pregnancy that had VeraCept exposure through delivery and at least 6 weeks post-delivery. Updated instruction for menstrual cup to include menstrual disc use. Updated record retention requirement. Corrected reference #1. Added subject initial and date line to IUD Removal Subject Numeric Pain Rating Scale (Appendix 3). Included administrative changes and clarifications.	E Gray	06.30.23

A Phase 3, Prospective, Multi-Center, Single-Arm, Open-Label Study to Evaluate VeraCept®, a Long-Acting Reversible Intrauterine Contraceptive for Contraceptive Efficacy, Safety, and Tolerability

Protocol Number:	CMDOC-0042
IND #:	119743
Version / Date:	Version 7.0 / 30 June 2023
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INVESTIGATOR'S AGREEMENT

I have received a copy of Protocol Number CMDOC-0042, A Phase 3, Prospective, Multi-Center, Single-Arm, Open-Label Study to Evaluate VeraCept®, a Long-Acting Reversible Intrauterine Contraceptive for Contraceptive Efficacy, Safety, and Tolerability, Version 7.0 dated June 30, 2023 from Sebela. I agree to the conditions as set out in this protocol and fully accept that any change requires prior approval from Sebela. Additionally, I agree to carry out all terms of this protocol in accordance with International Conference on Harmonization (ICH) Guidelines, all applicable US Regulations (21 Code of Federal Regulations [CFR] parts 50, 54, 56 and 312) and Good Clinical Practice (GCP) Guidelines, as applicable. Finally, I 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 / Institutional 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 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 Sebela, except to the extent necessary to obtain informed consent and assent, if applicable, from potential study participants.

Investigator's Name (print)

Investigator's Signature | Date (MM/DD/YYYY)

TABLE OF CONTENTS

List of In-Text Tables

List of In-Text Figures

Appendices

REVISION HISTORY

Version	Date	Justification for Revision
1.0	08/12/ 2017	Initial version
2.0	11/01/2017	FDA Feedback
3.0	06/15/2018	Removed the randomized sub-study
4.0	03/22/2019	To address Investigator Meeting and enrollment period feedback and questions
5.0	06/17/2019	Clarify exclusion criteria, clarify double barrier method, add menstrual cup use information, and update AE outcome definition
6.0	06/30/2021	Update Month 60 visit window. Updated VeraCept illustration referencing "Shape Memory Frame" and replaced with "Nitinol Frame" (Figure 1). Added Pandemic Response section. Added menstrual product use collection to study procedures. Added Pre-Removal Planning guidelines (Appendix 4) and VeraCept Removal Instructions (Appendix 5). Updated potential risk section. Changed "IUD" to "IUS" as appropriate. Changed "Introducer" to "Inserter" throughout. Provided administrative changes and clarifications. Updated Phase 2 study results. Combined Protocol Versions 4A and 5A into Version 6 (added exclusion #21a).
7.0	06/30/2023	Updated Sebela Pharmaceuticals, Inc. to Sebela Women's Health. Extended study duration to 8 years. Added additional study visits and analyses. Updated secondary endpoints and sample size. Added clarification for excluding subjects from the EP population. Updated potential risk section. Added a Subject Satisfaction Survey for subjects exiting study for years 6-8. Updated requirements for missed visits and discontinuing subjects as lost to follow-up. Updated timelines for collection of adverse events and concomitant medications. Added the need to follow any off-treatment pregnancy that had VeraCept exposure through delivery and at least 6 weeks post-delivery. Updated instruction for menstrual cup to include menstrual disc use. Updated record retention requirement. Corrected reference #1. Added subject initial and date line to IUD Removal Subject Numeric Pain Rating Scale (Appendix 3). Included administrative changes and clarifications.

INVESTIGATIONAL PLAN SUMMARY

Protocol Title:

A Phase 3, Prospective, Multi-Center, Single-Arm, Open-Label Study to Evaluate VeraCept®, a Long-Acting Reversible Intrauterine Contraceptive for Contraceptive Efficacy, Safety, and Tolerability

Protocol Number:

CMDOC-0042

Current Protocol Version:

Version 7.0 / June 30, 2023

Drug Name

VeraCept® Intrauterine Contraceptive (referred to as VeraCept or study drug throughout this document)

Study Design

Prospective, multi-center, single-arm, open-label, Phase 3 clinical study to 3 years with extension up to 8 years

Study Objectives

The primary objective of the study is to assess the contraceptive efficacy (prevention of pregnancy) of VeraCept.

The secondary objectives of the study are to assess the following for VeraCept:

- Safety and tolerability
- Return to fertility after VeraCept removal, only for subjects requesting VeraCept removal to become pregnant

Study Duration

Subject enrollment will take approximately 9 months.

VeraCept subjects will be followed for up to 8 years. Women requesting VeraCept removal for a desired pregnancy will be followed for up to one year after the IUS is removed. The total study duration for a subject being followed for return to fertility could be up to 9 years. Any on-treatment pregnancies or off-treatment pregnancies with exposure to VeraCept will be followed through delivery and for at least 6 weeks post-delivery.

Number of Subjects

Approximately 1,605 subjects will be enrolled into the study to receive VeraCept on an open label basis. It is planned that approximately 1,480 of the 1,605 VeraCept subjects will be up to 35-years of age, and the remaining 125 subjects will be in the 36 to 45-year age range.

Investigational Site Information

This study will be conducted at approximately 45 centers in the US.

Follow-up

Enrolled subjects will have:

- Physical Assessments (Office Visits)
    - Year 1: At Weeks 6, 13, 26 and 52
    - Years 2-8: Every 6 months for up to 8 years after VeraCept placement.
- Regular Follow-Up Contacts (Non-Office Visits) (e.g., via phone, email, etc.)
    - Years 1-3: Conducted monthly beginning at Week 17, except when there is a scheduled office visit, through Year 3.

Years 3-8: Additional visits will be conducted if necessary for safety issues.

Follow-up after study drug removal:

All subjects will be followed until 17-days post-IUS removal to confirm pregnancy did not occur within 7 days of VeraCept removal. All subjects will be required to use an alternative contraceptive for the first 14 days following VeraCept removal.

Follow-up for subjects desiring pregnancy:

Subjects requesting VeraCept removal to become pregnant will be followed for 1 year, until they decide to no longer try to conceive or they become pregnant, whichever comes first.

Follow-up for on-treatment pregnancy subjects:

Any on-treatment pregnancies or off-treatment pregnancies with exposure to VeraCept will be followed through delivery and for at least 6 weeks post-delivery. Any infant abnormalities should be reported.

Study Population

Post-menarcheal, pre-menopausal women up to age 45 years, who are at risk for pregnancy and who desire a long-term intrauterine contraceptive for birth control will be eligible for this study. Both parous and nulliparous women are eligible. Subjects must provide written informed consent and assent, if applicable, and meet the study subject selection criteria without any exclusions, as outlined in the Clinical Investigation Plan (CIP).

Study Endpoints

Primary Endpoint

The primary endpoint is the contraceptive efficacy through 3 years of use, as assessed by the Pearl Index. The Pearl Index will be calculated for Years 1, 2 and 3, as well as cumulatively through Year 3.

Secondary Endpoints

Secondary endpoints include:

Contraceptive Efficacy:

- Pearl Index at Years 4, 5, 6, 7 and 8, as well as cumulatively through Years 4, 5, 6, 7 and 8
- Pregnancy percentage by life table analysis (Kaplan-Meier) at Years 1, 2, 3, 4, 5, 6, 7 and 8
- Separate analyses will be performed only for the last 3 years of the study (Years 6-8) using the EP population. The cumulative Pearl Index for Years 6 to 8 will be calculated as well as the cumulative pregnancy percentage for Years 6 to 8 using a life table analysis (Kaplan-Meier).

Study Drug Placement:

- Ease of VeraCept placement
- Placement success

Safety:

- Serious adverse events (SAEs)
- Adverse events (AEs)
- Pelvic infection (pelvic inflammatory disease (PID) or endometritis)
- Ectopic pregnancies
- Uterine perforations
- Dysmenorrhea
- Abdominal pain
- Expulsion rates at Years 1, 2, 3, 4, 5, 6, 7 and 8

Tolerability:

- Bleeding and spotting patterns
- Insertion pain assessed immediately after insertion
- Continuation rates at Years 1, 2, 3, 4, 5, 6, 7 and 8
- Reasons for discontinuation

Return to Fertility

- Pregnancy rate in subjects who request VeraCept removal specifically to become pregnant. Subjects who desire pregnancy after having VeraCept removed will be followed for either 1 year, until they decide to no longer try to conceive or they become pregnant, whichever comes first.

Study Selection Criteria

Inclusion Criteria

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

1. Post-menarcheal, pre-menopausal females up to 45 years of age at the time of informed consent/assent and in good general health;
2. History of regular menstrual cycles defined as occurring every 21-35 days when not using hormones or prior to recent pregnancy or spontaneous or induced abortion;
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 months duration;
6. Seeking to avoid pregnancy for the duration of the study;
7. Willing to use the study drug as the sole form of contraception;
8. Willing to accept a risk of pregnancy;
9. Subjects must be in compliance with cervical cancer screening guidelines per the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines without evidence of disease. Subjects who are age 21-24 y/o, at time of informed consent, must have a normal Papanicolaou test (Pap), atypical squamous cells of undetermined significance (ASC-US), or low-grade squamous intraepithelial lesion (LSIL). Subjects who are 25 or older at the time of informed consent with ASC-US results, must also have a negative high-risk human papilloma virus (HPV) test result within the appropriate screen timeframe per American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines, and prior to the study IUS insertion. Alternatively, the subject must have had a colposcopy performed within the appropriate screen timeframe, and prior to the study IUS insertion that showed no evidence of dysplasia requiring treatment per ASCCP guidelines, or treatment was performed and follow-up at least 6 months after the treatment showed no evidence of disease by clinical evaluation;
10. Able and willing to comply with all study tests, procedures, assessment tools (including e-diary) and follow-up;
11. Able and willing to provide and document informed consent and Authorization for Release of Protected Health Information (PHI). Unemancipated subjects under 18 years old must provide assent and have written parental consent documented on the consent form consistent with local legal requirements;
12. Plan to reside within a reasonable driving distance of a research site for the duration of the study.
13. Subject agrees not to self-remove VeraCept

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 a 6-month period during use of VeraCept;
3. A previously inserted intrauterine system (IUS) that has not been removed by the time the study IUS is placed;
4. History of previous IUS complications, such as perforation, expulsion, or pregnancy with IUS in place;
5. Pain with current IUS;
6. Injection of hormonal contraceptive (e.g., Depo-Provera) within the last 10 months and has not had 2 normal menstrual cycles since the last injection;
7. Planned use of any non-contraceptive estrogen, progesterone or testosterone any time during study participation;
8. Exclusively breastfeeding before return of menses; lactating women will be excluded unless they have had 2 normal menstrual periods prior to enrollment;
9. Unexplained abnormal uterine bleeding (suspicious for a serious condition), including bleeding 4 weeks post-septic abortion or puerperal sepsis;
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-human chorionic gonadotropin (ß-hCG) levels, or related malignant disease;
13. Any congenital or acquired uterine anomaly that may complicate study drug placement, such as:
    - Submucosal uterine leiomyoma
    - Asherman's syndromes
    - Pedunculated polyps
    - Bicornuate uterus
    - Didelphus or uterine septa
14. Any distortions of the uterine cavity (e.g., fibroids), that, in the opinion of the investigator, are likely to cause issues during insertion, retention or removal of the IUS;
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 drug placement;
16. Untreated or unresolved acute cervicitis or vaginitis;
17. Known or suspected human immunodeficiency virus (HIV) infection or clinical AIDS;
18. Subjects who have an established immunodeficiency;
19. Known intolerance or allergy to any components of VeraCept including intolerance or allergy to nickel, titanium, or copper, and including Wilson's Disease;
20. Currently participating or planning future participation in a research study of an investigational drug or device during the course of this investigational study. Subject must have waited at least 30 days from exiting their last study prior to informed consent in this study;

21. Subject has been enrolled in a previous VeraCept or LevoCept study;
21a. Subject has been enrolled in a previous VeraCept or LevoCept study where VeraCept or LevoCept placement was successful or attempted (replaces exclusion #21 for PK sub-study subjects only);
22. Known or suspected alcohol or drug abuse within 12 months prior to the screening visit;
23. Any general health, mental 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;
24. Study staff or a member of the immediate family of study staff.
25. Subject is ≤4 weeks post-pregnancy (postpartum, spontaneous or induced abortion)

Note: VeraCept can be inserted on any day of the menstrual cycle using the first three criteria for the Centers for Disease Control and Prevention (CDC) U.S. Selected Practice Recommendations for Contraceptive Use, 2016 [1] guidance to avoid an undetected pregnancy (see the revised Box 2 below from the CDC Selective Practice Recommendations and a copy is located in the study reference manual provided to the site). If a subject has a previously inserted IUS and has pain from that IUS upon removal, then the insertion of VeraCept should not occur until the pain has resolved.

Post Pregnancy Guidelines
Subjects who were recently pregnant must have a urine pregnancy test performed no sooner than 4 weeks post-pregnancy. If a subject has not had 2 normal menses since the end of a pregnancy, the study IUS may be placed if her hCG is negative and she has been on a reliable method of contraception (e.g., pills, patch, ring) that was started within 2 weeks post-pregnancy or has been on this reliable method for 4 weeks. If the urine hCG is still positive, investigators can obtain two quantitative hCG tests that must demonstrate declining hCG values at least 1 day apart.

BOX 2. How to be reasonably certain that a woman is not pregnant[1]

A health care provider can be reasonably certain that a woman is not pregnant if she has no symptoms or signs of pregnancy and meets any one of the following criteria:

- is ≤7 days after the start of normal menses
- has not had sexual intercourse since the start of last normal menses
- has been correctly and consistently using a reliable method of contraception*

* If condoms are being used, a double barrier method must be used (e.g., condoms + spermicide).

Statistical Methods

Study Populations:

Intent To Treat (ITT): All subjects who underwent the study drug placement procedure, regardless of whether the study drug was successfully placed or not.

Safety: ITT subjects who had the study drug successfully placed.

Safety Subgroup (36-45 years): Subjects in the safety population who were between 36 to 45 years of age (inclusive) at enrollment.

Evaluable for Pregnancy (EP): ITT subjects who had VeraCept placed successfully and meet requirements 1, 2 and 3 below. Subjects must also meet either requirement 4 or requirement 5 to be part of the EP study population.

1. Be post-menarcheal up to 35 years of age (inclusive) at enrollment
2. Have at least one report of pregnancy status after being enrolled

3. Do not have pre-treatment pregnancy, which is defined as the estimated conception date being before the insertion date.

AND

4. Have at least 1 cycle of e-diary with intercourse and without any backup contraception or emergency contraception (EC)

OR

5. Have an on-treatment pregnancy, which is defined as the estimated conception date being on or after the insertion date and no more than 7 days after the VeraCept is removed or expelled.

Subjects with major protocol violations that are deemed to have had a material impact on the primary efficacy assessment will be excluded from EP analysis population. Exclusions based on major protocol deviations will be reviewed and approved by Sebela and its designee.

Evaluable for Cycle Control (ECYC): ITT VeraCept subjects with at least one cycle for which:

1. A pregnancy did not occur;

AND

2. There was an assessment of bleeding in the e-diary data.

Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is contraceptive efficacy through three years of use and will be analyzed using the Pearl Index with 95% confidence interval (CI) for women in the EP population. Cycles (defined as 28 days) during which no intercourse occurs, or backup methods of contraception (including emergency contraception) are used will be excluded from the primary analysis of the Pearl Index unless the subject had an on-treatment pregnancy in that cycle. If Cycle 1 is evaluable, it will be included in the analysis regardless of the timing of VeraCept insertion relative to the subject's last pre-insertion menses.

One year is defined as comprising thirteen 28-day cycles.

Secondary Endpoint Analyses

All secondary endpoint analyses in the study will be descriptive.

Contraceptive Efficacy

The Pearl Index will be calculated for Years 4, 5, 6, 7 and 8 as well as cumulatively through Years 4, 5, 6, 7 and 8.

A life table analysis (using Kaplan-Meier) of pregnancies will be performed for the EP population to present the cumulative pregnancy percentage for Years 1 through 8.

Separate analyses will be performed only for the last 3 years of the study (Years 6-8) using the EP population. The cumulative Pearl Index for Years 6 to 8 will be calculated as well as the cumulative pregnancy percentage for Years 6 to 8 using a life table analysis (Kaplan-Meier).

Study Drug Placement

The number and percentage of subjects with either a successful or unsuccessful placement will be summarized for the ITT and Safety populations. The ease of VeraCept placement will be summarized for the Safety population.

Safety and Tolerability

- Incidence of AEs and SAEs will be summarized for the ITT population, as well as for the Safety population for all subjects and the 36 to 45-year-old safety sub-population.

- Bleeding and spotting patterns will be summarized for the ECYC population for the first year of treatment by the number of days in each 28-day cycle with bleeding or spotting, bleeding only and spotting only.
- The insertion pain assessed immediately after insertion will be summarized.
- Cumulative VeraCept continuation rates for Years 1 through 8 will be summarized using Kaplan-Meier methods for the Safety population. The number and percentage of subjects with each reason for discontinuation will be summarized.
- Cumulative VeraCept expulsion rates for Years 1 through 8 will be summarized using Kaplan-Meier methods for the Safety population.

Return to Fertility

The number and percentage of subjects with each return to fertility response will be summarized for the Safety population.

Sample Size

Approximately 1,605 subjects will be enrolled on an open label basis. It is planned that 1,480 of the 1,605 VeraCept subjects will be in the up to 35-year age range and the remaining 125 subjects will be in the 36 to 45-year age range. It is expected that at least 40% of enrolled subjects will be nulliparous.

It is expected that 1,480 post-menarcheal VeraCept subjects up to age 35 will provide at least 620 women with at least 3 years of use of VeraCept. It is expected that the study will have 577 woman-years of use in Year 3 of the study who are evaluable for the Pearl Index analysis. This will allow for the Pearl Index calculation for Years 1, 2, and 3 of the study and for the cumulative 3 years to have an upper bound of the 95% confidence interval no more than 1 unit above the point estimate of the Pearl Index.

It is also expected that 1,480 post-menarcheal VeraCept subjects up to age 35 will provide at least 350 women with 5 years of use of VeraCept.

The 1,605 enrolled VeraCept subjects are expected to provide over 17,000 cycles (28-day cycles) of exposure in Year 1. Over 54,000 VeraCept cycles are expected to be collected during the course of the 5-year study.

The 1,605 enrolled VeraCept subjects are expected to provide at least 200 women with 8 years of use of VeraCept. Over 65,000 VeraCept cycles are expected to be collected during the course of the 8-year study. These 8-year projections assume that 10% of the subjects that complete 5-years of use will not consent to extending their use of VeraCept beyond Year 5.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AIDS	Acquired Immunodeficiency Syndrome
ASC-US	Atypical Squamous Cells of Undetermined Significance
ASCCP	American Society for Colposcopy and Cervical Pathology
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CRF	Case Report Forms
Cu	Copper
DSMB	Data and Safety Monitoring Board
EC	Emergency Contraception
eCRF	Electronic Case Report Form
ECYC	Evaluable for Cycle Control
EE	Efficacy Evaluable
EP	Evaluable for Pregnancy
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ß-hCG	ß-human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HSIL	High Grade Squamous Intraepithelial Lesion
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine System
LSIL	Low-grade Squamous Intraepithelial Lesion
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
Mth(s)	Month(s)
N/A	Not Applicable
OC	Oral Contraceptive(s)
Pap test	Papanicolaou Test
PHI	Protected Health Information
PID	Pelvic Inflammatory Disease
SAE	Serious Adverse Event
STD	Sexually Transmitted Diseases
US	United States
Wk(s)	Week(s)

1 INTRODUCTION

The VeraCept® Intrauterine Contraceptive ("VeraCept") is designed as a hormone free, low-dose, copper-releasing birth control method. In the US, there are over 62 million women in their child-bearing years, ages 15 to 44. Thirty-eight million of these women (62%) use some form of contraception. Thirty-one percent (31%) do not use or need contraception because they are either trying to get pregnant, are pregnant, are infertile or are not sexually active. Seven percent (7%) are at risk for unintended pregnancy because they are not using any contraceptive method [2].

Contraceptive options for the 38 million US women using contraception include permanent sterilization (tubal ligation or vasectomy in male partner), contraceptive implants, intrauterine systems (IUSs), 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% of women [3]. The CHOICE Study showed that the actual use pill failure rate is 20 times higher than the failure rate with IUSs [4, 5].

IUSs have high initial costs, and therefore early discontinuation rates have profound impact on their cost-effectiveness. The early rates of user dissatisfaction due to complications or side effects may be associated with the materials used and/or their design. The Paragard® Copper T380 IUS has been associated with complaints of increased bleeding, inter-menstrual bleeding, and cramping pain. The LNG-IUS (Mirena®) is also associated with early complaints of irregular bleeding patterns, cramping pelvic pain, and amenorrhea. First year discontinuation rates for copper IUSs in most studies range from 4-15% [6-8].

With high unintended pregnancy rates in the US (49%) [2], additional effective, safe and long-acting reversible contraceptives are needed. An IUS with low-dose copper that achieves high contraceptive effectiveness, minimizes side effects, and has improved mechanical advantages could offer an attractive option to women seeking effective protection against unintended pregnancy. We believe VeraCept embodies these advantages.

1.1 Clinical Experience with VeraCept

1.1.1 Pilot Study

A pilot study of VeraCept in a population of parous women demonstrated the safe use of the study drug in approximately 463 subjects total in 2 phases of the study, representing approximately 6,706 combined women-months (558 women-years) of experience.

In this time period, there were no serious adverse events (SAEs) due to the study drug or its placement. The discontinuation rate due to tolerability reasons was low. There were no intrauterine pregnancies over the course of the study, and a single SAE (an ectopic pregnancy) that was reported early in the first of 2 phases of the study.

VeraCept was successfully placed in all enrolled subjects with no peri-procedural adverse events (AEs) and without the use of anesthetics, pre-medication or mechanical dilatation. VeraCept, in this initial experience, satisfied the objectives of providing a safe, easy-to-place, conformable, low-dose copper contraceptive that is highly tolerated.

In the second confirmatory phase of the pilot study, the subject continuation rate was 90% at 10 months, with a 2% expulsion rate and a 3% discontinuation due to tolerability rate. The remaining 5% of subjects discontinued due to other reasons (e.g., the desire to get pregnant or inability to comply with study follow-up requirements.)

1.1.2 Blinded, Randomized, Comparative Study

Subsequent to the pilot study, a randomized, subject-blinded comparative study of VeraCept vs. the Optima T380S IUS was conducted in a population of parous women enrolled at a single site [9].

A total of 300 women were enrolled with 199 randomized to VeraCept and 101 to the Optima T380S control arm. Insertion was successful in 99% of all subjects. No subjects developed clinical infection or reported SAEs. Statistically significant improvements in subject continuation rates at 12 and 24 months were demonstrated with VeraCept compared to the control T380S IUS. Tolerability (pain and bleeding), study drug expulsion, and pain at insertion were also all statistically significantly improved with VeraCept versus T380S. One ectopic pregnancy was identified at the 12-month follow-up in a VeraCept user. No other pregnancies were diagnosed. With 297.3 and 132.4 woman-years, pregnancy rates were 0.3 and 0.0 per 100 woman-years for VeraCept and T380S, respectively.

1.1.3 Phase 2, Open-label, Single-Arm Study

A US Phase 2, multicenter, open-label, single-arm study (Protocol CMDOC-0008) was conducted to evaluate the effectiveness, study device placement, safety and tolerability of VeraCept at 12 months, with a 24-month extension phase to a total of 36-months study participation. The final 36-month analysis has been completed. A total of 286 subjects, parous and nulliparous premenopausal women between the ages of 18-40 years, were enrolled at 12 investigational sites in the US. VeraCept was successfully inserted in 283 subjects (99%). Placement was reported to be "easy" or "very easy" for 259/283 subjects (92%) in the safety population. At least some device placement pain was reported by 240/283 subjects (85%). Device placement pain was rated as "some pain" by 137/283 subjects (48%), "painful" by 49/283 subjects (17%), "moderately painful" by 42/283 subjects (15%), and "very painful" by 12/283 subjects (4%). Most subjects (86%) did not require mechanical dilation.

The one-year findings demonstrated that VeraCept was effective through 13 cycles of use: a single pregnancy was reported among the 250 subjects in the evaluable for pregnancy (EP) population, equating to a Pearl index of 0.52 (95% CI: 0.01, 2.87). By Kaplan-Meier analysis, the cumulative probability for remaining pregnancy free through Day 365 was 0.995.

The favorable safety, tolerability, and effectiveness data observed at one year in the Phase 2 study supported the initiation of the Phase 3 clinical trial for VeraCept.

Subjects were allowed to remain in the study, in the extension phase, for an additional 24 months and for a total of 36 months of study participation. Overall, 177/286 subjects (62%) chose to continue in the extension phase and of those, 107/177 subjects (60%) completed 36 months. The 36-month findings continue to demonstrate VeraCept's contraceptive efficacy. A second pregnancy occurred during the extension phase of the study, with a cumulative 3-year Pearl index for all EP subjects of 0.73 (95% CI: 0.09, 2.65).

VeraCept was shown to be easily placed by Investigators and was well tolerated by subjects with a safety and tolerability profile comparable to other intrauterine copper contraceptives. During the 36-month study duration, AEs led to discontinuation for 51/283 subjects (18%) and most were reported as mild or moderate in intensity. A total of 11 SAEs were reported in 10 subjects after 36 months of VeraCept use; 8 of these were assessed as unrelated by Investigators and 3 were deemed unlikely related (hemorrhagic ovarian cyst, ectopic pregnancy, and pelvic inflammatory disease). Therefore, the 36-month data for this Phase 2 study demonstrated VeraCept to be effective, safe, and well-tolerated as a long-acting intrauterine contraceptive (CMDOC-0008 Clinical Study Report).

2 STUDY DURATION

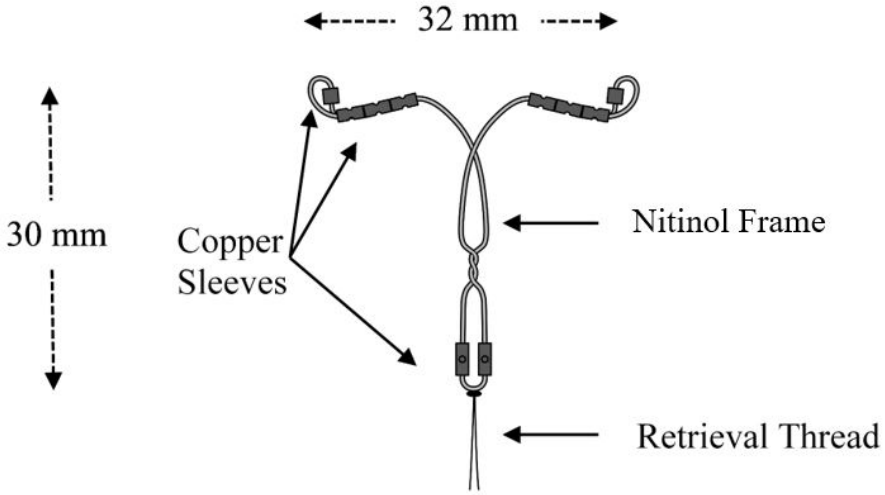
Subject enrollment will take approximately 9 months. Each VeraCept subject will be followed for up to 8 years. Women requesting VeraCept removal for a desired pregnancy may be followed for up to one year after the IUS is removed. The total study duration for a subject being followed for return to fertility could be up to 9 years. Any on-treatment pregnancies or off-treatment pregnancies with exposure to VeraCept will be followed through delivery and for at least 6 weeks post-delivery.

3 INVESTIGATIONAL PRODUCT DESCRIPTION

3.1 VeraCept

VeraCept is designed for use as a birth control method. The study drug consists of a nitinol spring with copper sleeves at both the distal arms and proximal stem. The study drug is shaped such that upon placement in the uterus, the nitinol spring positions itself at the fundus, with the copper sleeved arms near the ostia of the fallopian tubes and copper sleeved stem at or near the internal os of the cervix. Figure 1 illustrates the basic design and layout of the study drug.

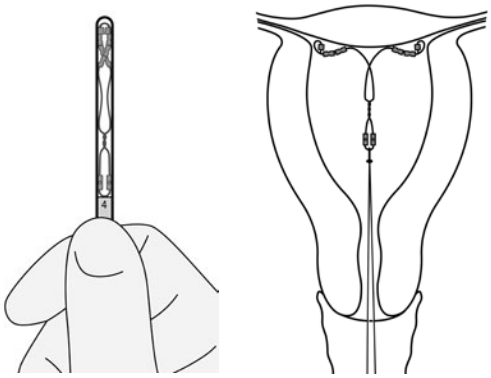
Figure 1: Schematic of VeraCept



The amount of copper utilized in VeraCept is 175 mm^2 exposed surface area. This compares to 380 mm^2 of copper surface area for the Paragard IUS. Because of its spring action, VeraCept can place concentrated amounts of copper in anatomically relevant positions within the uterus, which is designed to result in a more efficient elution profile for contraception. VeraCept is preloaded in an inserter that is used to place the sterile study drug in the uterus. VeraCept is retrieved with a standard monofilament polypropylene retrieval thread.

Figure 2 (left) shows the study drug in its pre-loaded state (directly from the package) in the distal end of the inserter. Figure 2 (right) shows a schematic of the study drug oriented in the uterus post placement.

Figure 2: Schematic of VeraCept in Pre-loaded State and Post-uterine Placement at Fundus



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 assent, if applicable, and Protected Health Information (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 IUS and pain is present from removal of the IUS, VeraCept insertion should not occur until the pain has resolved.

4.1 Dosage and Formulation

VeraCept contains 175 mm^2 of exposed copper surface area. A single VeraCept design and dosage will be used in this study. VeraCept will be supplied by Sebela. For further details, see the VeraCept Intrauterine Contraceptive Investigator's Brochure.

4.2 Supply and Administration

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

See the Investigator's Brochure for a more detailed VeraCept product description, and the VeraCept Clinician's Quick Guide for placement instructions.

4.3 Storage and Accountability

VeraCept should be stored at 25°C (77°F), with excursions permitted between -20°C to +50°C (-4°F to 122°F).

Study drug 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 for a detailed list of Investigator Responsibilities. All unused study drug will be stored for inventory and collection. The IUS may be analyzed for residual copper to estimate the rate of release of copper. All removed/used devices should be retained until further instructions from Sebela. Cleaning, storage, and shipping instructions are detailed in the Study Reference Manual.

4.4 Dosage Modifications

All subjects will receive the same VeraCept dosage of 175mm^2 exposed copper surface area. No study drug will be replaced if an expulsion or removal occurs.

4.5 VeraCept Placement Confirmation

Subjects will be instructed on how to check for the presence of the IUS by feeling for the strings in the vagina. Subjects will not be required to routinely check for the study IUS presence, but if a subject believes the study IUS may have been expelled or is no longer in place, the subject can check for the string if desired. If the subject does not feel the strings, feels more than the strings or has expelled the study IUS, the subject should be instructed to immediately call for an urgent study visit and refrain from having sex or use appropriate non-hormonal contraception until further evaluation is completed. In the event that the IUS strings cannot be located during a pelvic exam string check, a transvaginal ultrasound (TVUS) should be performed to confirm IUS presence and appropriate position. All transvaginal ultrasounds should be sent to the sponsor designated central reader to confirm

the results. If the IUS has been expelled, the subject should be discontinued; a new study IUS should not be inserted. If the strings are not visible or palpable in the vaginal cavity but the TVUS confirms adequate placement in the uterus, the subject may continue. At future visits if the IUS strings are not visible then a TVUS should be repeated to re-confirm placement.

4.6 VeraCept Removal

4.6.1 VeraCept Pre-Removal Planning Timing Guidelines

Prior to VeraCept removal, the Pre-Removal Planning Timing Guidelines (Appendix 4) must be considered to prevent unintended pregnancy after removal. It is important that VeraCept removal and the initiation of the next method of contraception occurs as per the pre-removal timing guidelines. If the subject is unable to or unwilling to comply with the pre-removal timing guidelines, it should be determined if the subject has had vaginal intercourse within 7 days prior to removal. If intercourse within 7 days prior to removal is confirmed, VeraCept removal and the Exit Visit should be rescheduled. If rescheduling is not possible, emergency contraception (EC) should be provided at time of removal if vaginal intercourse occurred within the EC effectiveness window. All subjects must be instructed to continue use of new contraception method for 14 days after removal. Subjects must be educated on the risks of pregnancy if the recommended pre-removal timing guidelines are not followed.

4.6.2 VeraCept Removal Procedure

Ensure all items needed for VeraCept removal are readily available, including additional tools that may be required for a difficult removal or a removal without visible threads (see Appendix 5).

Instructions for VeraCept removal are detailed in Appendix 5.

All removed/used devices should be retained until further instructions from Sebela. Cleaning, storage, and shipping instructions are detailed in the Study Reference Manual.

5 OBJECTIVES AND ENDPOINTS

5.1 Objectives

The primary objective of the study is to assess the contraceptive efficacy (prevention of pregnancy) of VeraCept.

The secondary objectives of the study are to assess the following for VeraCept:

- Safety and tolerability
- Return to fertility after VeraCept removal, only for subjects requesting VeraCept removal to become pregnant

5.2 Endpoints

Primary Endpoint

The primary endpoint is the contraceptive efficacy through 3 years of use, as assessed by the Pearl Index. The Pearl Index will be calculated for Years 1, 2 and 3 as well as cumulatively through Year 3.

Secondary Endpoints

Secondary endpoints include:

Contraceptive Efficacy

- Pearl Index at Years 4, 5, 6, 7 and 8 as well as cumulatively through Years 4, 5, 6, 7 and 8.
- Pregnancy percentage by life table analysis (Kaplan Meier) at Years 1, 2, 3, 4, 5, 6, 7 and 8.
- Separate analyses will be performed only for the last 3 years of the study (Years 6-8) using the EP population. The cumulative Pearl Index for Years 6 to 8 will be calculated as well as the cumulative pregnancy percentage for Years 6 to 8 using a life table analysis (Kaplan-Meier).

Study Drug Placement

- Ease of VeraCept placement
- Placement success

Safety

- Serious adverse events (SAEs)
- Adverse events (AEs)
- Pelvic infection (pelvic inflammatory disease (PID) or endometritis)
- Ectopic pregnancies
- Uterine perforations
- Dysmenorrhea
- Abdominal pain
- Expulsion rates at Years 1, 2, 3, 4, 5, 6, 7 and 8

Tolerability

- Bleeding and spotting patterns
- Insertion pain assessed immediately after insertion
- Continuation rates at Years 1, 2, 3, 4, 5, 6, 7 and 8

- Reasons for discontinuation

Return to Fertility

- Pregnancy rate in subjects who request VeraCept removal specifically to become pregnant. Subjects who desire pregnancy after having VeraCept removed will be followed for either 1 year, until they decide to no longer try to conceive or they become pregnant, whichever comes first.

The primary and secondary endpoints for the study will be reviewed after at least 200 subjects have completed 3 years of treatment to assess if the data supports the filing of an NDA for approval of an indication with 3 years of use. The data up to 8 years of treatment will be continually assessed to determine if the data supports additional NDA filings in order to extend the use of VeraCept beyond the initial planned 3 years of use.

6 BENEFITS AND RISKS

6.1 Potential Benefits

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

6.2 Potential Risks/Adverse Reactions

Evidence from prior clinical studies has demonstrated that the use of VeraCept has low rates of SAEs or AEs, and that pregnancy failure rates (intrauterine and ectopic pregnancy) have been low.

The following AEs have been reported in ≥2% of pooled subjects in the three VeraCept studies (CMDOC-0008, CMDOC-0042, and CMDOC-0045) through 3 years of use. AEs designated with an asterisk (*) indicates AEs that were considered at least possibly related to VeraCept and/or the VeraCept placement/removal procedure in ≥2% of pooled subjects. This list is in alphabetical order and not in order of increasing/decreasing occurrence:

- Abdominal distension
- Abdominal pain lower
- Abdominal pain upper
- Abdominal pain*
- Acne
- Anxiety
- Arthralgia
- Back pain*
- Bacterial vaginosis*
- Coital Bleeding*
- COVID-19
- Depression

- Device expulsion*
- Diarrhea
- Dizziness
- Dysmenorrhea*
- Dyspareunia*
- Fatigue
- Headache
- Heavy menstrual bleeding*
- Influenza
- Insomnia
- Intermenstrual bleeding*
- Ligament sprain
- Menometrorrhagia*
- Migraine
- Nasopharyngitis
- Nausea
- Oropharyngeal pain
- Ovarian cyst
- Pelvic discomfort*
- Pelvic pain*
- Pharyngitis streptococcal
- Post procedural discomfort*
- Post procedural hemorrhage*
- Procedural pain*
- Sinusitis
- Upper respiratory tract infection
- Urinary tract infection
- Vaccination complication
- Vaginal discharge*
- Vomiting
- Vulvovaginal mycotic infection

In addition, the following clinically significant adverse events have been reported in <2% of pooled subjects in the VeraCept studies:

- Uterine hemorrhage
- Anemia as a result of uterine hemorrhage, which may lead to the need for blood transfusion
- Ectopic pregnancy
- Ruptured ectopic pregnancy
- Increased risk of spontaneous abortion if pregnancy occurs with VeraCept in place. Remove VeraCept if pregnancy occurs.

- Pelvic infection (pelvic inflammatory disease, endometritis), which can lead to fallopian tubal damage leading to ectopic pregnancy or infertility, hysterectomy, sepsis and rarely death
- Uterine perforation, which may require laparoscopy or laparotomy to remove VeraCept from the peritoneal cavity
- Embedment, which may require additional in clinic procedures or surgical removal

There may also be risks that are unanticipated at this time. See the VeraCept Investigator's Brochure for a complete list of reported adverse events and additional information.

Although pregnancy is not considered an adverse event, there is a possible risk of becoming pregnant while using VeraCept.

In addition to the above known risks, the following additional adverse events have been reported in association with Paragard T380A IUS(16). Adverse events associated with the Paragard T380A IUS may be relevant because it is also a copper-based contraceptive. The severity or frequency of any of the following events, should they occur, is not expected to be any different with the use of VeraCept. These events are not in order of severity or frequency.

- Risks with Intrauterine Pregnancy: septic abortion, premature delivery, sepsis, septic shock and death if pregnancy occurs.
- Sepsis: Group A streptococcal infection has been reported; strict aseptic technique is essential during insertion

6.3 Minimization of Anticipated Risks

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

- Establishing eligibility criteria that exclude subjects who are at higher risk for experiencing an anticipated AE;
- Conducting extensive preclinical and clinical testing prior to the start of this Phase 3 clinical study;
- 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;
- Manufacture of VeraCept per Good Manufacturing Practice (GMP) guidelines;
- Selecting investigators with proper level of training and experience in placing IUSs;
- Ensuring adequate monitoring is performed to identify any safety issues associated with the study procedure and subjects;
- Regularly reviewing reported SAEs and AEs throughout the study and taking appropriate medical measures to resolve the adverse events;
- Utilizing a data and safety monitoring board (DSMB) to oversee safety and performance outcomes.
- Providing adequate study oversight to ensure compliance with GCP.

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. 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.

The study will utilize a DSMB to oversee safety and performance outcomes. The DSMB charter will include stopping criteria in the event an unacceptable rate of pregnancy is observed. The stopping criteria will be assessed by observing the lower bound of the 95% confidence interval of the cumulative pregnancy percentage (Kaplan-Meier) at the given timepoint (e.g., cycle 6) for the VeraCept treatment. If the lower bound of the 95% confidence interval is greater than the decision point for the given DSMB meeting, then the DSMB will recommend suspension of enrollment into the study until a thorough review of risks and benefits can be performed since subjects appear to be at a higher risk of pregnancy than expected. The decision point used for each DSMB meeting will depend upon how much data is expected to be available at the timepoint of interest (e.g., cycle 6) for the DSMB meeting. The timepoint used for the Kaplan-Meier analysis and the decision point for each DSMB meeting will be specified in the DSMB charter. The DSMB charter will detail the number and timing of DSMB reviews. The sponsor can request additional DSMB meetings if they have any concerns.

7 SELECTION AND TRAINING OF CLINICAL SITES AND INVESTIGATORS

The study will be conducted at approximately 45 centers in the US:

- Experience and adequate training in IUS use and conduct of regulated clinical studies
- Adequate facilities and equipment
- Adequate patient volume
- Appropriate personnel and site research staff to support the conduct of the study, and
- 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 Investigational Review Board (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 eCRFs provided by Sebela representative or designee.
- Review and are familiar with VeraCept Clinician's Quick Guide and Investigator Brochure.
- Complete training with VeraCept, provided by a Sebela 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 International Conference of Harmonization (ICH) E6 Good Clinical Practice (GCP) guidelines
- Compliance with the Declaration of Helsinki
- Compliance with IRB and local regulatory requirements

7.1 Laboratories

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

8 STUDY POPULATION

The study population will be post-menarcheal, pre-menopausal women up to 45 years of age, who are at risk for pregnancy and who desire a long-term intrauterine contraceptive for birth control. Both parous and nulliparous women are eligible.

Subjects must provide written informed consent and assent, if applicable, and meet the study entry criteria noted below.

8.1 Inclusion Criteria

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

1. Post-menarcheal, pre-menopausal females up to 45 years of age at the time of informed consent/assent and in good general health;
2. History of regular menstrual cycles defined as occurring every 21-35 days when not using hormones or prior to recent pregnancy or spontaneous or induced abortion;
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 months duration;
6. Seeking to avoid pregnancy for the duration of the study;
7. Willing to use the study drug as the sole form of contraception;
8. Willing to accept a risk of pregnancy;
9. Subjects must be in compliance with cervical cancer screening guidelines per the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines without evidence of disease. Subjects who are age 21-24 y/o, at time of informed consent, must have a normal Papanicolaou test (Pap), atypical squamous cells of undetermined significance (ASC-US), or low-grade squamous intraepithelial lesion (LSIL). Subjects who are 25 or older at the time of informed consent with ASC-US results, must also have a negative high-risk human papilloma virus (HPV) test result within the appropriate screen timeframe, and prior to study IUS insertion. Alternatively, the subject must have had a colposcopy performed within the appropriate screen timeframe per American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines, and prior to study IUS insertion that showed no evidence of dysplasia requiring treatment per ASCCP guidelines, or treatment was performed and follow-up at least 6 months after the treatment showed no evidence of disease by clinical evaluation;
10. Able and willing to comply with all study tests, procedures, assessment tools (including e-diary), and follow-up;
11. Able and willing to provide and document informed consent and Authorization for Release of Protected Health Information (PHI). Unemancipated subjects under 18 years old must provide assent and have written parental consent documented on the consent form consistent with local legal requirements;
12. Plan to reside within a reasonable driving distance of a research site for the duration of the study;
13. Subject agrees not to self-remove VeraCept;

8.2 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 a 6-month period during use of VeraCept;
3. A previously inserted IUS that has not been removed by the time the study IUS is placed;
4. History of previous IUS complications, such as perforation, expulsion, or pregnancy with IUS in place;
5. Pain with current IUS;
6. Injection of hormonal contraceptive (e.g., Depo-Provera) within the last 10 months and has not had 2 normal menstrual cycles since the last injection;
7. Planned use of any non-contraceptive estrogen, progesterone or testosterone any time during study participation;
8. Exclusively breastfeeding before return of menses; lactating women will be excluded unless they have had 2 normal menstrual periods prior to enrollment
9. Unexplained abnormal uterine bleeding (suspicious for a serious condition), including bleeding 4 weeks post-septic abortion or puerperal sepsis;
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-human chorionic gonadotropin (ß-hCG) levels, or related malignant disease;
13. Any congenital or acquired uterine anomaly that may complicate study drug placement, such as:
    - Submucosal uterine leiomyoma
    - Asherman's syndromes
    - Pedunculated polyps
    - Bicornuate uterus
    - Didelphus or uterine septa
14. Any distortions of the uterine cavity (e.g., fibroids), in the opinion of the investigator, are likely to cause issues during insertion, retention or removal of the IUS;

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 drug placement;

16. Untreated or unresolved acute cervicitis or vaginitis;

17. Known or suspected human immunodeficiency virus (HIV) infection or clinical AIDS;

18. Subjects who have an established immunodeficiency;

19. Known intolerance or allergy to any components of VeraCept; including intolerance or allergy to nickel, titanium, or copper, and including Wilson's Disease;

20. Currently participating or planning future participation in a research study of an investigational drug or device during the course of this investigational study. Subject must have waited at least 30 days from exiting their last study prior to informed consent in this study;

21. Subject has been enrolled in a previous VeraCept or LevoCept study;

21a. Subject has been enrolled in a previous VeraCept or LevoCept study where VeraCept or LevoCept placement was successful or attempted (replaces exclusion #21 for PK sub-study subjects only);

22. Known or suspected alcohol or drug abuse within 12 months prior to the screening visit;

23. Any general health, mental 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;

24. Study staff or a member of the immediate family of a study staff.

25. Subject is $\leq$4 weeks post-pregnancy (postpartum, spontaneous or induced abortion)

Note: VeraCept can be inserted on any day of the menstrual cycle using the first three criteria for the Centers for Disease Control and Prevention (CDC) U.S. Selected Practice Recommendations for Contraceptive Use, 2016 [1] guidance to avoid an undetected pregnancy (see Box 2 the revised below from the CDC Selective Practice Recommendations and a copy is located in the study reference manual provided to the site). If a subject has a previously inserted IUS and has pain from that IUS removal, then the insertion of VeraCept should not occur until the pain has resolved.

8.3 Post Pregnancy Guidelines

Subjects who were recently pregnant must have a urine pregnancy test performed no sooner than 4 weeks post-pregnancy. If a subject has not had 2 normal menses since the end of a pregnancy, the study IUS may be placed if her hCG is negative and she has been on a reliable method of contraception (e.g., pills, patch, ring) that was started within 2 weeks post-pregnancy or has been on this reliable method for 4 weeks. If the urine hCG is still positive,

investigators can obtain two quantitative hCG tests that must demonstrate declining hCG values at least 1 day apart.

BOX 2. How to be reasonably certain that a woman is not pregnant[1]

A health care provider can be reasonably certain that a woman is not pregnant if she has no symptoms or signs of pregnancy and meets any one of the following criteria:

- is ≤7 days after the start of normal menses
- has not had sexual intercourse since the start of last normal menses
- has been correctly and consistently using a reliable method of contraception*

* If condoms are being used, a double barrier method must be used (e.g., condoms + spermicide).

9 INFORMED CONSENT

The person obtaining 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); for those subjects under 18 years, assent should be obtained, and informed consent documented from a parent or legal guardian, consistent with local legal requirements.
- 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 impact on her ability to obtain other services;
- Ensure protection of the candidate's confidentiality; and
- Provide a copy of the Informed 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 and assent form, if applicable, including the Authorization for Release of Protected Health Information (PHI) form and the Subject Bill of Rights form (where applicable). The sponsor or designee must review and approve the IRB approved informed consent form and assent form, prior to any subject enrollment. The investigator or designee must review the informed consent form, assent form (if applicable), PHI form and

Bill of Rights form (where applicable) with the candidate in her native language and explain all study risks and benefits and answer all patient questions before obtaining the candidate's signature on the informed consent form and assent form. All subjects must provide written informed consent/assent in accordance with local law and approved by the site's (or Central) IRB. The PHI and Subject Bill of Rights forms (where applicable) must also be signed by the candidate prior to study participation.

10 ENROLLMENT

A subject is considered enrolled into the study after signing the informed consent and assent, if applicable, PHI, and Bill of Rights forms (where applicable), and being found eligible based on her history, physical examination and screening tests, and a VeraCept insertion attempt. Eligible consented subjects who withdraw consent/assent for any reason before an IUS insertion attempt will be considered screen failures.

11 STUDY SCHEDULE OF ASSESSMENTS

A schedule of assessments for all VeraCept subjects is provided in Table 1.

Table 1: Study Schedule of Assessments

		Screen	Years 1-8					Other	
		Screening	Enrollment (VeraCept Placement) Day 1	Office Visits: W 6 ± 1 w W 13 ± 1w W 26 ± 2w W 52 ± 2w	Regular Contact[9]: W 17, 21, 30, 34, 39, 43, 47 ±1w Monthly M13-17, M19-23, M25-29, M31-35 (±1 w)	Office Visits: M 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90 (± 1 m)	M 96 + 1 m or Exit Visit	Contact to confirm pregnancy for those desiring pregnancy[8]	30-Day Post-Removal AE follow-up
Initiation/ Subject Characteristics	Assessment of Eligibility	X	X						
	Distribution of subject materials, if applicable	X							
	Informed consent and assent, if applicable, PHI and Bill of Rights forms (where applicable)	X							
	Demographics and baseline characteristics	X							
	Med/surgical, gynecological and menstrual history	X							
Safety and Efficacy	Vital signs and weight	X	X	X		X	X		
	Height	X							
	General physical exam	X					X		
	Pelvic exam (string check if post IUS insertion)	X	X[1]	X[1]		X[1]	X[1]		
	Cervical cytology	X							
	Cervical infection tests	X[5,7]							
	Transvaginal ultrasound[2]		X[2]	X[2]		X[2]	X[2]		
	Pregnancy test-urine	X	X	X		X	X[4]		
	Prior and concurrent medication	X	X	X	X	X	X		
	Adverse events		X	X	X	X	X		X[16]
Other	Contact IWRS	X[12]	X[13]				X		
	IUD placement		X						
	IUD placement ease		X						
	IUD placement pain (11-point scale)		X[10]						
	IUD removal						X[14,15]		
	IUD removal ease						X		
	IUD removal pain (11-point scale)						X[11]		
	Concomitant contraception		X	X	X	X	X[14]		
	Subject education - need for contraception	X	X	X	X	X	X		
	Subject e-Diary training and re-training	X[3a]	X	X	X	X			
	e-Diary reviewed with subject[6]		X[3a]	X[3b]	X[3b]	X[3b]	X[3b]		
	Discontinued Subject Desiring Pregnancy							X[8]	
	Subject satisfaction survey						X[17]		

Note: The screening and enrollment visits may be combined if all protocol procedures are complete and entry criteria are met.

Footnotes

1. Pelvic exam for VeraCept string check by palpation or visualization
2. Transvaginal Ultrasound only if clinically indicated (e.g., to confirm adequate IUS placement)
3a. This first e-diary review, prior to VeraCept placement, to be used as training with the subject. This diary data is not part of data collection or analysis. It is intended to ensure the subject understands how to complete the diary and determine subject compliance throughout e-diary collection.
3b. Review for completeness. If not complete, subject to enter information, if within 7- day open timeframe. Remind the subject to complete diary contemporaneously.
4. Urine pregnancy test will be done at the Month 96 or exit visit and 17 days after removal/study exit by the subject at home, with a required follow up call by the study coordinator or PI to obtain and document the results.
5. Screening for cervical infection tests are to be done at screening unless these tests have been previously completed within 3 months of the screening visit and were negative. If a subject tests positive prior to VeraCept insertion, the subject should be treated prior to VeraCept placement. A cervical infection re-test should be done 3-months post-treatment to confirm cure.
6. Subjects will complete an e-diary through Month 96 and will receive detailed instructions on how to complete the daily e-diary. From Month 13 – Month 96, only other contraceptive use, intercourse, adverse events and concomitant medications will be recorded on the e-diary by the subject.
7. Insertion can occur without receipt of test results if there is no clinical evidence of infection. If after VeraCept insertion the screening cervical infection test results are positive, the subject should be treated and retested 3 months post-treatment to confirm cure.
8. Subjects who prematurely discontinue from the study and are desiring pregnancy will be followed for either 1 year, 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 by contacting the subject (e.g., phone, email, etc.) and documented in the source document and eCRF.
9. Contact subject (e.g., via phone, email, etc.). Starting at Week 17 from day of VeraCept insertion.
10. See Appendix 2 for the IUD Insertion Subject Numeric Pain Rating Scale
11. See Appendix 3 for the IUD Removal Subject Numeric Pain Rating Scale
12. Upon receipt of informed consent and assent, if applicable, contact the IWRS to register the subject, initiate the subject's screening diary and obtain a subject number
13. Contact the IWRS prior to insertion to obtain an enrollment number, the IUS dispensation assignment, and initiate the enrollment diary. If an IUS insertion is a failure, contact the IWRS to record the IUS insertion failure and to obtain a second IUS dispensation assignment or to discontinue the subject
14. See Appendix 4 for Pre-Removal Planning Timing
15. See Appendix 5 for Removal Instructions
16. An additional contact will be performed 30 days post-removal or expulsion for any AEs that were ongoing at the time of VeraCept removal. If the date of expulsion is unknown the additional contact will be performed 30 days after the date of expulsion discovery.
17. Subjects completing at least 6 years (72 months) of study will complete a Subject Satisfaction Survey at the Exit Visit.

12 STUDY PROCEDURES

12.1 Pandemic Response (e.g., COVID-19)

Ensuring the safety of trial participants is paramount. The sponsor will consider the need to modify study conduct in response to pandemic-related circumstances to maintain the safety of trial participants and data integrity, as necessary [10].

12.2 Screening

The following must be completed prior to VeraCept placement:

- Subject meets inclusion and exclusion criteria
- Informed Consent and assent, if applicable, PHI, and Bill of Rights (where applicable) forms signed
- Upon receipt of informed consent and assent, if applicable, contact the IWRS to register the subject, initiate the subject's screening diary and obtain a subject number
- 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
    - Head, eyes, ears, nose and throat (HEENT)
    - Thyroid
    - Lungs
    - Back
    - Breasts
    - Heart
    - Abdomen
    - Extremities
    - Neurological
- Pelvic exam
- For subjects who are age 21-24 y/o, at time of informed consent, the subject must have a normal Papanicolaou test (Pap), atypical squamous cells of undetermined significance (ASC-US), or low-grade squamous intraepithelial lesion (LSIL). Subjects who are 25 or older, at the time of informed consent with ASC-US results, must also have a negative high-risk human papilloma virus (HPV) test result within the appropriate screen timeframe, and prior to IUS insertion. Alternatively, the subject must have had a colposcopy performed within the appropriate screen timeframe per American Society for Colposcopy and Cervical Pathology (ASCCP)

guidelines, and prior to IUS insertion that showed no evidence of dysplasia requiring treatment per ASCCP guidelines, or treatment was performed and follow-up at least 6 months after the treatment showed no evidence of disease by clinical evaluation;

- Cervical infection tests (gonorrhea and chlamydia) should be performed per one of the following options:
    - A participant with negative results obtained within 3 months of the screening visit does not need further testing.
    - Insertion can occur without receipt of test results if there is no clinical evidence of infection. If after the study IUS insertion, the screening cervical infection test results are positive, the subject should be treated and retested 3 months post-treatment to confirm cure.
    - If a subject tests positive within 6 months prior to the study IUS insertion, the subject should be treated prior to the study IUS placement. The subject may be inserted 7 days post-treatment. A cervical infection retest should be done 3 months post-treatment.
- Urine pregnancy test
- Prior and concurrent medications
- Need for contraception (review and discuss the subject's need for appropriate contraception during the screening period)
- Train subject on e-diary use and completion and provide e-diary instructions. Diary entries from the screening visit to study drug insertion are for training purposes and will not be included in data analysis. 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.

12.3 VeraCept Placement/ Enrollment (Day 1)

VeraCept can be inserted on any day of the menstrual cycle using the first three criteria for the Centers for Disease Control and Prevention (CDC) U.S. Selected Practice Recommendations for Contraceptive Use, 2016 [1] as guidance to avoid an undetected pregnancy (see the revised Box 2 below from the CDC Selective Practice Recommendations and a copy is located in the study reference manual provided to the site).

Post Pregnancy Guidelines

Subjects who were recently pregnant must have a urine pregnancy test performed no sooner than 4 weeks post-pregnancy. If a subject has not had 2 normal menses since the end of a pregnancy, the study IUS may be placed if her hCG is negative and she has been on a reliable method of contraception (e.g., pills, patch, ring) that was started within 2 weeks post-pregnancy or has been on this reliable method for 4 weeks. If the urine hCG is still positive, investigators can obtain two quantitative hCG tests that must demonstrate declining hCG values at least 1 day apart.

BOX 2. How to be reasonably certain that a woman is not pregnant[1]

A health care provider can be reasonably certain that a woman is not pregnant if she has no symptoms or signs of pregnancy and meets any one of the following criteria:

- is ≤7 days after the start of normal menses
- has not had sexual intercourse since the start of last normal menses
- has been correctly and consistently using a reliable method of contraception*

* If condoms are being used, a double barrier method must be used (e.g., condoms + spermicide).

Subjects must have a negative urine pregnancy test immediately prior to VeraCept placement. VeraCept insertion is consistent with standard IUS placement. Refer to the Clinician's Quick Guide and Investigator's Brochure for specific instructions.

If placement is unsuccessful, a second attempt may be made on the same day or within 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 VeraCept 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 eCRF. The need for prophylactic pain medication to control IUS insertion pain will also be left to the discretion of the investigator per institutional practice guidelines and the subject. Any medications given for pain control will be recorded on the Concomitant Medications eCRF. The use of misoprostol prior to VeraCept insertion is not recommended except where needed, at the discretion of the Investigator [11].

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

- Entry criteria confirmed
- Contact the IWRS to obtain an enrollment number, the IUS dispensation assignment, and initiate the enrollment diary
- Vital signs and weight
- Pelvic exam
- Urine pregnancy test
- Prior and concurrent medications
- Assess for any changes in health status
- Review the completed practice e-diaries and discuss with the subject any further training and answer any questions the subject may have about how to correctly complete the e-diaries. Review for change in health status and concomitant medications.

Following VeraCept placement, the following will be performed:

- VeraCept placement ease

- VeraCept placement pain. The subject completes the IUD Insertion 11- point Subject Numeric Pain Rating Scale immediately after IUS insertion (see Appendix 2)
- Pelvic exam (string check)
- Transvaginal ultrasound if unable to confirm adequate placement
- Concurrent medications
- Adverse events
- Type(s) of menstrual products subject currently uses
- If there are concerns that VeraCept is not properly placed, counsel the subject on the need for additional contraception
- Counsel the subject that if at any time, she believes the study drug may have been expelled or is no longer in place, the subject should call immediately for an urgent study visit and refrain from having sex or use appropriate non-hormonal contraception until further evaluation is completed. (See Section 4.5 for details)
- If an IUS insertion is a failure, contact the IWRS to record the IUS insertion failure and to obtain a second IUS dispensation assignment or to discontinue the subject.

If a subject has failed two drug placement attempts, she will not be replaced.

12.4 Office Visits: Week 6 ±1Wk, 13 ±1Wk, 26 ±2Wks, and 52 ±2Wks from VeraCept Insertion

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

- Vital signs and weight
- Type(s) of menstrual products subject has used since the last visit
- Pelvic exam (string check)
- Transvaginal ultrasound to document VeraCept position, if clinically indicated
- Urine pregnancy test
- Interval and concurrent medications
- Adverse events
- Counsel the subject that if at any time, she believes the study drug may have been expelled or is no longer in place, the subject should call immediately for an urgent study visit and refrain from having sex or use appropriate non-hormonal contraception until further evaluation is completed. (See Section 4.5 for details)
- E-diary review with subject:
    - Review for completeness. If not complete, subject to enter information, if within 7- day open timeframe. Remind the subject to complete diary contemporaneously.
    - Verify sexual activity and if any back-up contraception method is documented
    - Review subject's diary and assess for adverse events
    - Re-education on e-diary completion, if needed

- Subject recorded adverse events
- Subject recorded interval and concurrent medications

12.5 Regular Contact: Weeks 17, 21, 30, 34, 39, 43, 47 ±1Wk and Monthly at months 13-17, 19-23, 25-29, 31-35 ±1Wk from VeraCept Insertion

Subjects will be contacted (e.g., via phone, email, etc.) starting at Week 17 from day of VeraCept insertion until Month 35 (Year 3), to review:

- Interval and concomitant medications;
- Adverse events
- Use of concomitant contraception;
- Counsel the subject that if at any time, she believes the study drug may have been expelled or is no longer in place, the subject should call immediately for an urgent study visit and refrain from having sex or use appropriate non-hormonal contraception until further evaluation is completed. (See Section 4.5 for details)
- E-diary review with subject:
  - Review for completeness. If not complete, subject to enter information, if within 7- day open timeframe. Remind the subject to complete diary contemporaneously.
  - Verify sexual activity and if any back-up contraception method is documented
  - Review subject's diary and assess for adverse events
  - Re-education on e-diary completion, if needed
  - Subject recorded adverse events
  - Subject recorded interval and concurrent medications

12.6 Office Visits: Months 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90 ±1Month from VeraCept Insertion

Starting at Month 18 from VeraCept insertion the subject will return for follow-up visits every 6 months through Month 90 (Year 8). At these follow-up visits, the following will be performed:

- Vital signs and weight
- Type(s) of menstrual products subject has used since the last visit
- Pelvic exam (string check)
- Transvaginal ultrasound to document VeraCept position, if clinically indicated
- Urine pregnancy test
- Interval and concurrent medications
- Adverse events
- Use of concomitant contraception;
- Counsel the subject that if at any time, she believes the study drug may have been expelled or is no longer in place, the subject should call immediately for an urgent

study visit and refrain from having sex or use appropriate non-hormonal contraception until further evaluation is completed. (See Section 4.5 for details)

- E-diary review with subject:
    - Review for completeness. If not complete, subject to enter information, if within 7- day open timeframe. Remind the subject to complete diary contemporaneously.
    - Verify sexual activity and if any back-up method is documented
    - Review subject's diary and assess for adverse events
    - Re-education on e-diary completion, if needed.
    - Subject recorded adverse events
    - Subject recorded interval and concurrent medications

12.7 Month 96 +1 Month from VeraCept Insertion and/or Exit Visit

- Prior to VeraCept removal, the Pre-Removal Planning Timing guidelines (Appendix 4) must be considered to prevent unintended pregnancy after removal. It is important that VeraCept removal and the initiation of the next method of contraception occurs as per the timing guidelines. Subjects must be educated on the risks of pregnancy if the recommended guidelines are not followed (see Section 4.6).
- Vital signs and weight
- Type(s) of menstrual products subject has used since the last visit
- General physical exam
- Pelvic exam (string check)
- Transvaginal ultrasound to document VeraCept position, if clinically indicated
- Urine pregnancy test
- Interval and concurrent medications
- Adverse events
- E-diary review with subject:
    - Review for completeness. If not complete, subject to enter information, if within 7- day open timeframe.
    - Verify sexual activity and if any back-up method is documented
    - Review subject's diary and assess for adverse events
    - Subject recorded adverse events
    - Subject recorded interval and concurrent medications
- Subject Satisfaction Survey (only for subjects completing at least 6 years (72 months) of study)
- If a subject was unable to or unwilling to comply with the Pre-Removal Planning Timing guidelines (Appendix 4), it should be determined if the subject has had vaginal intercourse within 7 days prior to removal. If confirmed, VeraCept removal and the Exit Visit should be rescheduled. If rescheduling is not possible, emergency

contraception (EC) should be provided at time of removal if vaginal intercourse occurred within the EC effectiveness window.

- VeraCept Removal (see Appendix 5 for Removal Instructions)
  - VeraCept removal ease
  - VeraCept removal pain. The subject completes the IUD Removal 11- Point Subject Numeric Pain Rating Scale immediately after IUS removal (see Appendix 3)
  - The IUS may be analyzed for residual copper to estimate the rate of release of copper. All removed/used devices should be retained until further instructions from Sebela. Cleaning, storage, and shipping instructions are detailed in the Study Reference Manual.
- The subject's preferred method of contraception will be provided:
  - 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, a one-month supply of hormonal contraceptive pills will be provided to the subject by the site for the first 14 days following VeraCept removal
  - All subjects must be provided with a 14-day supply of condoms at time of removal (unless a new IUS is inserted)
  - All subjects must be instructed to continue use of new contraception method for 14 days after removal.
- Subjects should be reminded to avoid conception within 7 days after VeraCept removal
- Contact the IWRS to update the subject status
- Urine pregnancy test will be done 17 days after removal/study exit by the subject at home, with a required follow up call by the study coordinator or PI to obtain and document results
- An additional contact will be completed 30 days after VeraCept removal for any Adverse Events that remain ongoing at the time of IUS removal or expulsion. If the date of the expulsion is unknown the additional contact will occur 30 days after the date of expulsion discovery. AE stop date and outcome are required to be updated, if applicable.

12.8 Allergic Reaction or Hypersensitivity to Components of VeraCept

If a subject experiences allergy-related symptoms or a hypersensitivity reaction (e.g., urticarial allergic skin reaction, rash) while VeraCept is placed, she should be assessed for a possible allergy to the components of VeraCept (nickel, titanium, and copper). A clinician will determine the historical relationship between symptoms and IUS use to inform a determination of causality. As needed, a nickel, titanium, and/or copper patch test will be performed and/or an assessment by a specialist for VeraCept users. If the IUS is determined to be the cause or highly suspected of causing the allergic reaction or hypersensitivity, the

IUS should be removed, and the AE(s) must be followed until resolution, the condition stabilizes, 30 days post study drug removal, or the subject dies or is lost to follow up (including withdrawal of consent/assent), whichever occurs first.

12.9 Discontinuation Visit

All subjects will be required to use an alternative contraceptive for the first 14 days following VeraCept removal, as described in Section 12.7.

12.9.1 Early Discontinuation due to an AE

If a subject requests VeraCept removal because of an AE, the Study Exit Visit (see Section 12.7) should be completed and documented on the CRF at the time of IUS removal. The subject will be followed until resolution of the event or 30 days after removal, whichever occurs first.

12.9.2 Early Discontinuation for Subjects who want to Attempt Pregnancy

If a subject requests VeraCept removal to become pregnant, the Study Exit Visit (Section 12.7) should be completed and documented on the CRF at the time of VeraCept removal. Subjects should avoid pregnancy within the 7 days post IUD removal. Additionally, subjects will be followed for either: 1 year or until they decide to no longer try to conceive or they become pregnant, whichever comes first. Outcome data regarding the subject's ability to conceive, or the decision to no longer try to become pregnant will be collected by contacting the subject (e.g., via phone, email, etc.) and documented in the source document and eCRF.

12.9.3 Early Discontinuation due to IUS Expulsion

Subjects exiting the study due to IUS expulsion should have a Study Exit Visit (Section 12.7), which should be completed and documented on the CRF. See Section 12.11 for instructions for pregnancy mitigation.

12.10 Unscheduled Visits

Unscheduled visits will be documented in the source and the CRFs. Medical evaluations will be conducted as indicated by the reason for the unscheduled visit.

12.11 IUS Expulsion

If the subject suspects the IUS has been expelled, she should contact the study site immediately. The subject should be scheduled for a visit as soon as possible and counseled to refrain from having sex or use appropriate non-hormonal contraception. Emergency contraception may be administered (e.g., ella® (preferred) or Plan B One-Step® based on provider and participant counseling and choice), according to product labelling, if the subject suspects that expulsion has occurred, and an act of intercourse might be unprotected, and she does not want the risk of pregnancy. A transvaginal ultrasound should be performed to confirm IUS presence and appropriate position, if clinically indicated. If the IUS is expelled, the subject will be exited from the study. The expulsion should be recorded as an AE on the CRF.

12.12 Missed Visits and Lost to Follow-Up

12.12.1 Missed Visits

All reasonable efforts should be made to ensure that enrolled subjects return to the investigational site for all study visits. Any subject who misses a scheduled visit or monthly contact follow-up should have contact attempts by the study staff as follows:

- At least three documented attempts to contact the subject (e.g., via phone, text, e-mail, mail, etc.). Method of contact attempts should vary.
- If the subject cannot be contacted or is contacted and still fails to come in for a scheduled visit, a follow-up letter must be sent via email AND certified letter (unless a previous certified letter was returned as undeliverable).

Attempts to contact the subject should continue as described above for each missed visit. A visit is considered missed once the following visit window opens. The missed visit should be recorded as "visit not done" in the EDC.

12.12.2 Lost to Follow-Up

A lost to follow-up subject is a subject who does not come in for an exit visit/VeraCept removal at the time of study completion and their final status outcome is unknown. Study completion is defined as Month 60 (Year 5) for subjects who did not consent to the extension study and Month 96 (Year 8) for those who did consent to the extension study.

Subjects not returning for an exit visit but who provide a final status are not considered lost to follow-up (e.g., device removed by outside provider, withdrew consent, refused VeraCept removal, etc.). Every effort should be made to retrieve VeraCept for final study drug disposition.

Subjects previously designated as lost to follow-up under the prior lost to follow-up guidance (protocol Amendment version 6.0 or earlier) will be required to be contacted annually until the visit window for Month 60 (Year 5) has closed. Refer to Study Reference Manual for additional instructions.

Subjects discontinued as lost to follow-up who later resume contact with the site should be requested to come in for device removal or confirmation of removal and with a request to return VeraCept, if possible (see CCGs for instructions on updating the CRFs).

13 E-DIARIES

Subjects will be instructed to complete e-diaries daily. Training and detailed instructions on how to complete the e-diary will be provided to subjects. The screening period will be used to train the subjects on how to use the e-diary and to assess the subject's e-diary completion compliance. The diary data collected during the screening period will not be used in the analysis. Subjects will have up to 7 days to input e-diary data for each day. During subject visits and contacts, the site should review the e-diary with the subject to assess for e-diary completion. In addition, all e-diary entries should be reviewed and assessed for adverse

events and concomitant medications. Subjects should be re-educated if they are not completing the diary or are incorrectly completing it. E-diaries are designed to collect the following information for each day of the 28-day cycle from Screening through Month 12:

- Day of cycle
- Date
- Absence or presence of scheduled (menstrual) or unscheduled (intermenstrual) vaginal bleeding/spotting (none, spotting, light bleeding, normal bleeding or heavy bleeding)
- Vaginal intercourse
- IUD expulsion (yes, no, suspected)
- Usage of additional birth control methods and type of birth control used
- Presence of menstrual pain or cramping
- Adverse events
- Concomitant medications

Vaginal bleeding categories are defined as follows:

- None: no bleeding or spotting
- Spotting: a minimal amount of vaginal bleeding and only one panty liner is used all day or did not use any protection (panty liner, pad, tampon)
- Light bleeding: have vaginal bleeding and one or two pads or tampons are used, or more than one panty liner is used, throughout the day
- Medium bleeding: have vaginal bleeding and three or four pads or tampons are used throughout the day
- Heavy bleeding: have a large amount of vaginal bleeding and more than four pads or tampons are used throughout the day

From Month 13 – Month 96 the following will be collected:

- Day of cycle
- Date
- Vaginal intercourse
- IUD expulsion (yes, no, suspected)
- Usage of additional birth control methods and type of birth control used
- Adverse events
- Concomitant medications

14 CONCOMITANT MEDICATIONS AND DEVICES

Concomitant medications include any medication (any prescription medications or over the counter preparations) taken from the time the subject signs the informed consent/assent

documents until VeraCept removal/ expulsion or medications used to treat reportable SAEs occurring after study drug removal and must be recorded appropriately on the eCRF. In addition, concomitant medications used as prior contraception or used to treat a prior cervical infection within 30 days of informed consent/assent should also be reported.

14.1 Prohibited Concomitant Medications

- The use of misoprostol prior to the study IUS insertion is not recommended except where needed, at the discretion of the Investigator [11].
- The use of contraceptive or non-contraceptive estrogen, progesterone, testosterone or gonadotropin (e.g., hCG) is not allowed during the study.
- Medications that require the use of double barrier contraception (e.g., Isotretinoin - brand names Absorica®, Accutane®, Amnesteem®, Claravis®, Myorisan®, Sotret®, and Zenatane™).
- Any other birth control method that could potentially affect the results of this study should not be used during study participation. However, if the subject believes she will be at risk for an STD, then she should use a condom for protection.
- Any other investigational treatment or medication other than VeraCept, unless approved by the sponsor.
- Subjects who begin to chronically use excluded therapies or illegal drugs may be discontinued from the study. Investigators must contact the Medical Monitor to discuss possible discontinuation of these subjects.
- Subjects should be instructed to abstain from using menstrual cups and discs to avoid accidental IUS removal during menstrual cup and disc removal. Menstrual cup and disc use may dramatically increase the likelihood of unintentional IUS expulsion and should not be used. If a subject cannot be discouraged from using a menstrual cup or disc, ensure the subject is familiar with the menstrual cup and disc instructions for use for proper insertion and removal. It is recommended that placement be low in the vagina and not in contact with the cervix. Should a menstrual cup or disc user notice that the cup or disc is in contact with the cervix the recommendation is to pinch the edge of the cup or disc first to break the seal of the cup or to avoid pulling the IUD strings that may be in contact with the disc and then removing the cup or disc.

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 situation (subject is at immediate risk of death);
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect in the offspring of a subject who received study drug; 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 AE (i.e., a new event or an exacerbation of a pre-existing condition) with an onset from the day of informed consent/assent through VeraCept removal or expulsion should be recorded as an AE on the eCRF. An event that is discovered during the screening visit that clearly started or was acquired prior to obtaining informed consent (e.g., positive cervical infection test, positive cervical pathology) should be recorded as medical history and not as an AE. All AEs must be recorded regardless of the severity or relationship to study drug. 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 AE in this study.

15.3 Adverse Events of Special Interest

Adverse events of particular clinical importance, other than SAEs will be classified as adverse events of special interest (AESIs). For this study, AESIs refer to reports of pain during insertion, pelvic infection (PID or endometritis), dysmenorrhea, abdominal pain, expulsion and uterine perforation. AESIs will be identified and assessed by the Medical

Monitor during the ongoing monitoring of safety data during the trial, during DMSB meetings and for the Clinical Study Report. For each AESI, a narrative may be written and included in the Clinical Study Report.

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

An Investigator who is qualified in medicine must make the determination of relationship to the drug for each AE. The relationship of an AE to the drug should be assessed using the guidelines presented in Table 2. An AE for which there has been no causal relationship reported initially will require follow-up to determine causality. Of the definitions in Table 2, "possibly", "probably" and "related" to an investigational medical product are considered adverse reactions. "Unlikely" and "not related" do not qualify as a causal relationship.

Table 2: Adverse Event Relationship to Drug

Relationship to Drug	Description
Related	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis
Probably related	The adverse event: • Follows a reasonable temporal sequence from the time of study drug administration; *and/or* • Follows a known response pattern to the study drug; *and* • Was unlikely to have been produced by other factors such as the subject's clinical state, therapeutic intervention, or concomitant therapy
Possibly related	The adverse event: • Follows a reasonable temporal sequence from the time of study drug administration; *and/or* • Follows a known response pattern to the study drug; *but* • Could have been produced by other factors such as the subject's clinical state, therapeutic intervention, or concomitant therapy
Unlikely related	The adverse event: • Does not follow a reasonable temporal sequence from the time of study drug administration; *and* • Was likely produced by other factors such as the subject's clinical state, therapeutic intervention, or concomitant therapy but for which relationship cannot be definitely ruled out
Not related	The adverse event can be determined with certainty to have no relationship to the study drug

15.4.1 Clarification of Adverse Events Related to Study Procedures

Any untoward event that occurs from the time of informed consent/assent, including the study drug 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 drug placement procedure." If the AE also meets the criteria for an SAE, an SAE report should be completed and submitted to the sponsor.

15.5 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 usually 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.

15.6 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.

Not Recovered/Not Resolved: At the time of the last assessment, the event is ongoing. 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.

Unknown: The Adverse Event outcome is unknown due to the subject becoming lost to follow-up or the subject withdraws consent and is unwilling to provide outcome

information. The outcome of "Unknown" should not be used if the subject is still active in study and/or is willing to provide outcome information.

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 report. 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 report. If an SAE report is completed, pertinent laboratory data should be recorded on the SAE report, preferably with baseline values and copies of laboratory reports.

15.7 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 IUS 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;
- 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 report 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 drug 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.

15.8 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 drug placement or that are present at baseline and worsen following placement of IUS 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.

15.9 Documenting Adverse Events

Any AE occurring from the time of informed consent/assent through VeraCept removal or expulsion 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 report 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.

15.10 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 drug removal or expulsion, or the subject dies or is lost to follow-up (including withdrawal of consent/assent), whichever occurs first. The investigator is responsible for

ensuring 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.

15.11 Clarification in Reporting of Deaths

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

15.12 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 drug placement through VeraCept removal or expulsion require reporting to the sponsor. In addition, if the investigator learns of any SAE at any time after a subject has had the study drug removed, and such event seems reasonably related to study drug, the investigator should immediately notify the sponsor.

15.13 IUS or Inserter Malfunction

Should the IUS or its inserter not perform mechanically as expected, the sponsor should be informed. Details of the malfunction will be collected, and the sponsor will determine if the IUS and/or inserter should 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 Sebela 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 Sebela and its designee, according to the 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 Sebela or its designee, or a violations/deviation may be identified after the fact, by the investigator, Sebela, or the monitoring staff. Investigators will be asked to provide an explanation for all violations and deviations identified. Sebela, 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/assented to allow access to her data, as described during the informed consent process and documented in the signed informed consent/assent form. Each subject will also sign an Authorization for Release of Protected

Health Information (PHI) form granting Sebela 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/assent 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 ON-TREATMENT PREGNANCY DETERMINATION AND FOLLOW UP

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

Subjects will be counseled and followed for at least 6-weeks post-delivery, and the clinical outcome will be recorded. Any infant abnormalities should be reported.

See Pregnancy Reporting Guidelines in Study Reference Manual (Appendix 7) for additional instructions.

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 drug and study drug 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 the study IUS 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 drug, adverse study drug 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 3 dates: 2 years

after study completion, 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 drug 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 VeraCept only to qualified investigators. The investigator shall maintain adequate records of the receipt and disposition of all VeraCept IUSs. The investigator shall return any unused drug, opened or unopened, to the sponsor or its designees when enrollment has completed. All removed/expelled IUSs or IUSs contaminated during a failed insertion attempt should be stored on site until accountability can be performed and/or until return or destruction is approved by Sebela. If given approval to destroy IUS on site, dispose per institutional policy.

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 drug, 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 or inspection, 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.

The primary and secondary endpoints for the study will be reviewed after 200 subjects have completed 3 years of treatment to assess if the data supports the filing of an NDA for approval of an indication with 3 years of use. The data up to 8 years of treatment will be continually assessed to determine if the data supports additional NDA filings in order to extend the use of VeraCept beyond the initial planned 3 years of use.

20.1 Analysis Populations

The following analysis populations will be created:

- **Intent to Treat (ITT):**
  All subjects who underwent the study drug placement procedure, regardless of whether the study drug was successfully placed or not.
- **Safety:**
  ITT subjects who had the study drug successfully placed
- **Safety Subgroup (36-45 years):**
  Subjects in the safety population who were between 36 to 45 years of age (inclusive) at enrollment.
- **Evaluable for Pregnancy (EP):**
  ITT subjects who had VeraCept placed successfully and meet requirements 1, 2 and 3 below. Subjects must also meet either requirement 4 or requirement 5 to be part of the EP study population:

  1. Be post-menarcheal up to 35 years of age (inclusive) at enrollment
  2. Have at least one report of pregnancy status after being enrolled
  3. Do not have pre-treatment pregnancy, which is defined as the estimated conception date being before the insertion date.

AND

  4. Have at least 1 cycle of e-diary with intercourse and without any backup contraception or emergency contraception (EC)

OR

  5. Have an on-treatment pregnancy, which is defined as the estimated conception date being on or after the insertion date and no more than 7 days after the VeraCept is removed or expelled.

  Subjects with major protocol violations that are deemed to have had a material impact on the primary efficacy assessment will be excluded from EP analysis population. Exclusions based on major protocol deviations will be reviewed and approved by Sebela and its designee.

- **Evaluable for Cycle Control (ECYC):**
  ITT VeraCept subjects with at least one cycle for which:

  1. A pregnancy did not occur;

AND

2. There was an assessment of bleeding reported by the subject.

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 ITT population.

20.3 Demographic and Other Subject Characteristics

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

20.4 Extent of Exposure

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

20.5 Pre-Trial and Concomitant Medications

Concomitant medications include any medication (any prescription medications or over the counter preparations) taken from the time of informed consent/assent until VeraCept removal/expulsion or medications used to treat reportable SAEs occurring after study drug removal. Pre-trial medications include any contraception used or treatment for a prior cervical infection within 30 days of informed consent/assent. 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 Endpoint Analysis

The primary efficacy endpoint in the study is contraceptive efficacy through three years of use and will be analyzed using the Pearl Index with 95% confidence interval for women in the EP population. Cycles (defined as 28 days) during which no intercourse occurs, or backup methods of contraception (including emergency contraception) are used will be excluded from the primary analysis of the Pearl Index unless the subject had an on-treatment pregnancy in that cycle. If Cycle 1 is evaluable, it will be included in the analysis regardless of the timing of VeraCept insertion relative to the subject's last pre-insertion menses.

One year is defined as comprising thirteen 28-day cycles.

20.7 Secondary Endpoint Analysis

All secondary endpoint analyses in the study will be descriptive.

20.7.1 Contraceptive Efficacy

The Pearl Index will be calculated for Years 4, 5, 6, 7 and 8, as well as cumulatively through Years 4 through 8.

A life table analysis (using Kaplan-Meier) of pregnancies will be performed for the EP population to present the cumulative pregnancy percentage for Years 1 through 8. As with the primary endpoint analysis, cycles with backup contraception or no intercourse will be excluded from the analysis and the remaining cycles will be compressed to provide contiguous cycles. A sensitivity analysis will be performed without excluding those cycles with backup contraception or no intercourse to assess the results without the need to compress cycles.

Separate analyses will be performed only for the last 3 years of the study (Years 6-8) using the EP population. The cumulative Pearl Index for Years 6 to 8 will be calculated as well as the cumulative pregnancy percentage for Years 6 to 8 using a life table analysis (Kaplan-Meier).

20.7.2 Study Drug Placement

The number and percentage of subjects with either a successful or unsuccessful placement will be summarized for the ITT and Safety populations. The ease of VeraCept placement will be summarized for the Safety population.

20.7.3 Safety and Tolerability

The following safety and tolerability analyses will be performed:

- Incidence of AEs and SAEs will be summarized for the ITT population as well as for the Safety populations for all subjects and the 36 to 45-year-old safety sub-population. The number and percentage of subjects with each AE and SAE will be presented in a table by MedDRA system-organ class and preferred term. Summaries will be presented by relationship to VeraCept and/or VeraCept placement or removal procedure and the severity of the adverse event. All AEs will be summarized, including these AESIs:
  - Pain during insertion
  - Pelvic infection (PID or endometritis)
  - Expulsion
  - Uterine perforation
  - Dysmenorrhea
  - Abdominal pain
- Bleeding and spotting patterns will be summarized (per Mishell [12]) for the ECYC population for the first year of treatment by the number of days in each 28-day cycle with bleeding or spotting, bleeding only and spotting only.
- The insertion pain assessed immediately after insertion will be summarized..
- Cumulative VeraCept continuation rates for Years 1 through 8 will be summarized using Kaplan-Meier methods for the Safety population. The number and percentage of subjects with each reason for discontinuation will be summarized.
- Cumulative VeraCept expulsion rates at for Years 1 through 8 will be summarized using Kaplan-Meier methods for the Safety population.

20.7.4 Return to Fertility

The number and percentage of VeraCept subjects with each return to fertility response will be summarized for the Safety population.

20.8 Data and Safety Monitoring Board

The study will utilize a data and safety monitoring board (DSMB) to oversee safety and performance outcomes (stopping rules will be further defined in the DSMB charter). The stopping criteria will be assessed by observing the lower bound of the 95% confidence interval of the cumulative pregnancy percentage (Kaplan-Meier) at the given timepoint (e.g., cycle 6) for the VeraCept treatment. If the lower bound of the 95% confidence interval is greater than the decision point for the given DSMB meeting, then the DSMB will recommend suspension of enrollment into the study until a thorough review of risks and benefits can be performed since subjects appear to be at a higher risk of pregnancy than expected. The decision point used for each DSMB meeting will depend upon how much data is expected to be available at the timepoint of interest (e.g., cycle 6) for the DSMB meeting. The timepoint used for the Kaplan-Meier analysis and the decision point for each DSMB meeting will be specified in the DSMB charter. The DSMB charter will detail the number and timing of DSMB reviews. The sponsor can request additional DSMB meetings if they have any concerns.

20.9 Determination of Sample Size

Approximately 1,605 subjects will be enrolled on an open label basis. It is planned that 1,480 of the 1,605 VeraCept subjects will be in the up to 35-year age range and the remaining 125 subjects will be in the 36 to 45-year age range. It is expected that at least 40% of enrolled subjects will be nulliparous.

It is expected that 1,480 post-menarcheal VeraCept subjects up to age 35 years will provide at least 620 women with at least 3 years of use of VeraCept. It is expected that the study will have 577 woman-years of use in Year 3 of the study who are evaluable for the Pearl Index analysis. This will allow for the Pearl Index calculation for Years 1, 2, and 3 of the study and for the cumulative 3 years to have an upper bound of the 95% confidence interval no more than 1 unit above the point estimate of the Pearl Index.

It is also expected that 1,480 post-menarcheal VeraCept subjects up to age 35 years will provide at least 350 women with 5 years of use of VeraCept.

The 1,605 enrolled VeraCept subjects are expected to provide over 17,000 cycles (28-day cycles) of exposure in Year 1. Over 54,000 VeraCept cycles are expected to be collected during the course of the 5-year study.

The 1,605 enrolled VeraCept subjects are expected to provide at least 200 women with 8 years of use of VeraCept. Over 65,000 VeraCept cycles are expected to be collected during the course of the 8-year study. These 8-year projections assume that 10% of the subjects that complete 5-years of use will not consent to extending their use of VeraCept beyond Year 5.

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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:

1. Have the resources to conduct the investigation properly
2. Ensure that conducting the investigation will not give rise to a conflict of interest
3. Obtain from the sponsor the information which the investigator(s) judges essential about the study drug and be familiar with this information
4. Be well acquainted with the protocol before signing it
5. 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
6. Discuss with the sponsor management any question or modification of the protocol
7. 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.
8. Make the necessary arrangements to ensure the proper conduct and completion of the investigation
9. Make the necessary arrangements for emergency treatment, as needed, to protect the health and welfare of the subject
10. Ensure that appropriate IRB approvals are obtained prior to the start of the investigation
11. Provide the communication from the IRB to the study sponsor
12. Inform the IRB about any serious adverse drug effects in accordance with the IRB requirements.
13. Inform the sponsor about any adverse events and adverse drug effects in a timely manner and in accordance with the timelines laid out in this protocol
14. Endeavor to ensure an adequate recruitment of subjects
15. Ensure that the subject has adequate time and information to give informed consent/assent and that parents or legal guardians also have adequate time and information to provide parental informed consent when needed per local legal requirements.

16. Ensure that informed consent authorization to release protected health information is obtained and documented prior to any study specific evaluations or procedures being performed
17. Ensure that clinical records are clearly marked to indicate that the subject is enrolled in this study
18. Provide subjects with well-defined procedures for any emergency situation and safeguard the subject's interest
19. 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
20. Inform the subject (and subject's parent/legal guardian as required) 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
21. Have primary responsibility for the accuracy, legibility and security of all investigational data, documents and subject records both during and after the investigation
22. Review and sign each subject's eCRFs (last page only)
23. Be responsible for the supervision and assignment of duties at his/her study center
24. Ensure that all investigational drug is accounted for (number of IUSs used, discarded and returned to the sponsor)
25. 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
26. 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
27. Ensure that the investigator discloses to the sponsor if the investigator has ever been barred from conducting or participating in clinical research.

Appendix 2: IUD Insertion Subject Numeric Pain Rating Scale

Protocol CMDOC-0042
IUD Insertion
Subject 11-Point Numeric Pain Rating Scale

Site Instructions

The subjects should rate the pain they experienced during IUD placement immediately after IUD insertion.

Subject Instructions

On a scale from 0 – 10, circle the number that best describes the amount of pain you experienced when the IUD was placed in your uterus.

0	1	2	3	4	5	6	7	8	9	10
No pain					**Moderate pain**					**Worst possible pain**

Appendix 3: IUD Removal Subject Numeric Pain Rating Scale

Protocol CMDOC-0042
IUD Removal
Subject 11–Point Numeric Pain Rating Scale

Site Instructions

The subjects should rate the pain they experienced during IUD removal immediately after IUD removal. Pain scale should be completed by subject.

Subject Instructions

On a scale from 0 – 10, circle the number that best describes the amount of pain you experienced when the IUD was removed from your uterus.

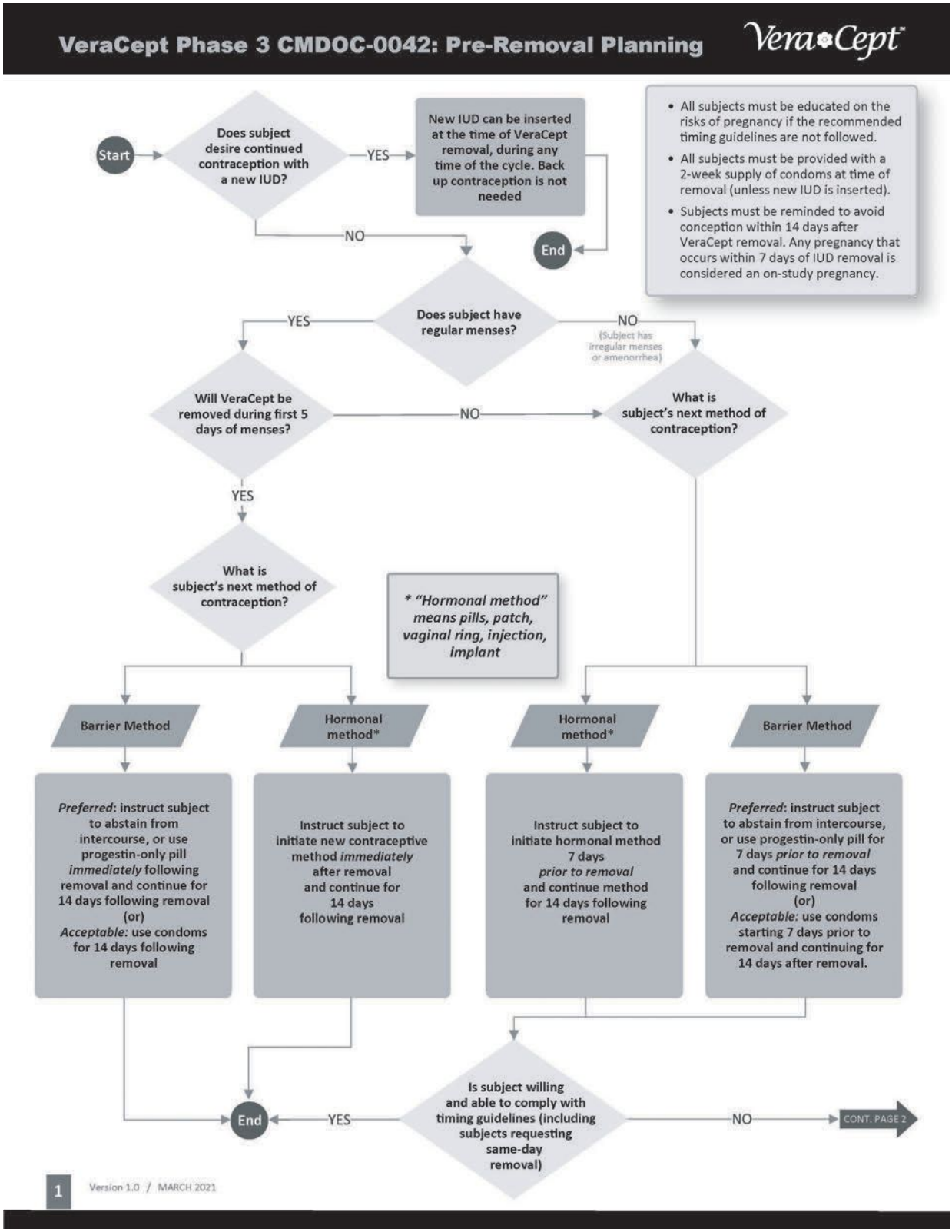
0	1	2	3	4	5	6	7	8	9	10
No pain					**Moderate pain**					**Worst possible pain**

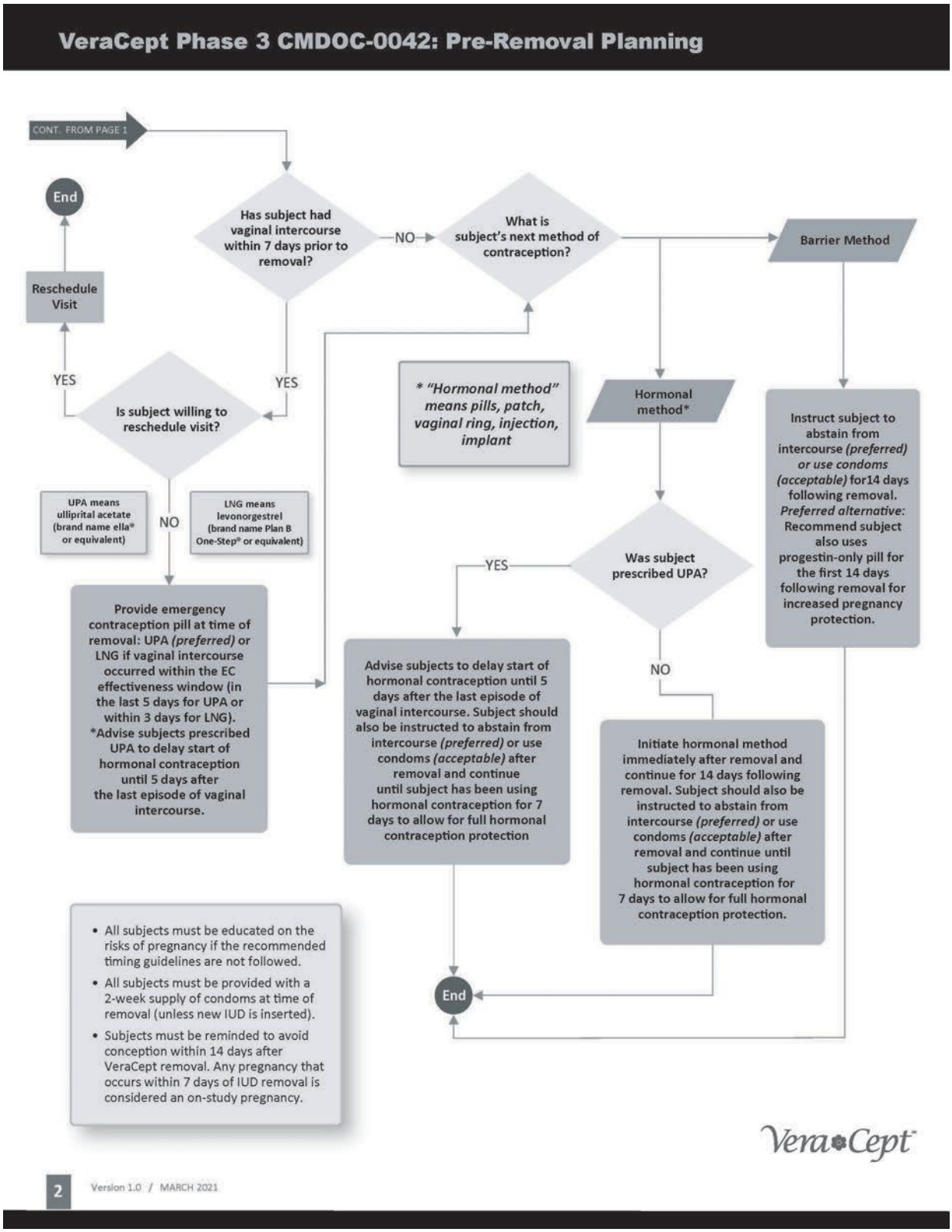
To be completed by Subject:

_____ _____

Subject Initials Date

Appendix 4: Pre-Removal Planning Timing Guidelines




VeraCept Phase 3 CMDOC-0042: Pre-Removal Planning
CONT. FROM PAGE 1
End
Has subject had vaginal intercourse within 7 days prior to removal?
NO
What is subject's next method of contraception?
Barrier Method
Reschedule Visit
YES
YES
Is subject willing to reschedule visit?
* "Hormonal method" means pills, patch, vaginal ring, injection, implant
Hormonal method*
Instruct subject to abstain from intercourse (preferred) or use condoms (acceptable) for14 days following removal. Preferred alternative: Recommend subject also uses progestin-only pill for the first 14 days following removal for increased pregnancy protection.
UPA means ulliprital acetate (brand name ella® or equivalent)
NO
LNG means levonorgestrel (brand name Plan B One-Step® or equivalent)
YES
Was subject prescribed UPA?
Provide emergency contraception pill at time of removal: UPA (preferred) or LNG if vaginal intercourse occurred within the EC effectiveness window (in the last 5 days for UPA or within 3 days for LNG). *Advise subjects prescribed UPA to delay start of hormonal contraception until 5 days after the last episode of vaginal intercourse.
Advise subjects to delay start of hormonal contraception until 5 days after the last episode of vaginal intercourse. Subject should also be instructed to abstain from intercourse (preferred) or use condoms (acceptable) after removal and continue until subject has been using hormonal contraception for 7 days to allow for full hormonal contraception protection
NO
Initiate hormonal method immediately after removal and continue for 14 days following removal. Subject should also be instructed to abstain from intercourse (preferred) or use condoms (acceptable) after removal and continue until subject has been using hormonal contraception for 7 days to allow for full hormonal contraception protection.
End
• All subjects must be educated on the risks of pregnancy if the recommended timing guidelines are not followed.
• All subjects must be provided with a 2-week supply of condoms at time of removal (unless new IUD is inserted).
• Subjects must be reminded to avoid conception within 14 days after VeraCept removal. Any pregnancy that occurs within 7 days of IUD removal is considered an on-study pregnancy.
VeraCept
2
Version 1.0 / MARCH 2021

Appendix 5: VeraCept Removal Instructions

VERACEPT REMOVAL PLANNING

Ensure all needed items for VeraCept removal are readily available.

Tools for Removal

- Gloves
- Speculum
- Long sterile forceps

Additional items that may be required for a difficult removal or a removal without visible threads:

- Ultrasound with abdominal probe
- Antiseptic solution
- Local anesthetic, needle, and syringe
- Sterile tenaculum
- Sterile os finder and/or cervical dilators
- Sterile long, narrow forceps, such as an alligator forceps, narrow polyp forceps, or long curved Kelly clamp
- Sterile intrauterine thread retriever

VERACEPT REMOVAL PROCEDURE

NOTE: Retain all removed/used devices until further instructions from Sebela. Cleaning and storage instructions are detailed in the Study Reference Manual (Section 6.6.1).

Removal Situation(s)	Instructions
When the threads are visible, then:	• With the subject comfortably in lithotomy position, place a speculum and visualize the cervix. o With long forceps, grasp the exposed threads close to the cervical os. o Remove VeraCept by applying gentle traction on the threads with forceps. o After removal of VeraCept, examine the device to ensure that it is intact*. **NOTE**: Removal may be associated with some pain and/or bleeding or vasovagal reactions (for example, syncope, bradycardia) or seizure, especially in people with a predisposition to these conditions.

Removal Situation(s)	Instructions

If you encounter significant resistance when applying traction on the threads with the forceps or if you are able to bring the device into the cervical canal but no further, then:	• Cleanse the cervix with antiseptic (chlorhexidine or povidone iodine).
	• While continuing to hold the threads steady with the forceps consider sliding a second sterile, narrow forceps (an alligator forceps, narrow polyp forceps, or long curved Kelly clamp) into the endocervical canal to grasp the lower portion of VeraCept.
	• Once you have purchase on the stem of the device with the second forceps, apply gentle traction to remove VeraCept.
	• If it becomes necessary to pass the narrow forceps through the internal os, strongly consider placing a cervical block (anesthesia). This will require use of a tenaculum and possibly dilation of the cervical canal and/or ultrasound guidance.
	• If VeraCept cannot be removed using the above techniques, consider use of hysteroscopy.
	• Contact the Sebela national PI for consultation:
	  o If you have concern regarding embedment
	  o If you would like consultation regarding a challenging removal
	  o If you have reason to believe that the device will not be able to be retrieved with a hysteroscope.
	• After removal of VeraCept, examine the device to ensure that it is intact*

If the threads are not visible, then:	Determine the location of VeraCept by ultrasound.
	
	• If the device is not visualized in the uterine cavity, obtain a KUB radiograph or CT to evaluate if the device is in the abdominal cavity.
	  o If it is suspected that the study device has been translocated into the abdominal cavity, manage appropriately and immediately notify the Sebela national PI.
	  o If the device is not visualized radiographically, it is presumed to have expelled
	  ▪ If device is expelled, follow protocol guidance for expulsions (i.e., ensure back-up contraception is provided, emergency contraception if intercourse occurred within the EC effectiveness window)
	• If VeraCept is found to be in the uterine cavity on ultrasound exam, place a speculum, visualize the cervix and apply antiseptic to the cervix.
	  o Use a sterile narrow forceps (such as an alligator forceps, narrow polyp forceps, or long curved Kelly clamp) or a thread retriever.

Removal Situation(s)	Instructions
	o Initially, attempt to grasp the strings within the cervical canal. o If the position of the device within the uterus requires that you pass the instrument into the uterine cavity, it is recommended that you place a cervical block and use a tenaculum. Consider use of dilation of the cervical canal and ultrasound guidance as needed. o If VeraCept cannot be removed using the above techniques, consider use of hysteroscopy.
***After removal of VeraCept, examine the device to ensure that it is intact.**	• If the device does not appear to be intact or if any defects are discovered (e.g., broken strings, device broke upon removal): o Retain the device o Notify the medical monitor immediately to determine if further assessment or analysis is needed