NCT03633799

Statistical Analysis Plan

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: 25 Jun 2018

STATISTICAL ANALYSIS PLAN

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
Protocol Version / Date:	3.0 / 15 June 2018
Sponsor:	Sebela Pharmaceuticals Development LLC 645 Hembree Parkway, Suite I Roswell, GA 30076
SAP Version:	3.0
SAP Date:	25 June 2018
Previous Version:	Draft 1.0, 15 August 2017 Draft 2.0, 17 November 2017

CONFIDENTIAL

STATISTICAL ANALYSIS PLAN

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Protocol Number: CMDOC-0042

SAP Version/Date: 3.0 / 25JUNE2018

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REVISION HISTORY

Version	Date	Reason for Revision
1.0	15AUG2017	Incorporated sponsor's comments and changed in the new protocol dated August 12, 2017 Notable changes per comments: • added definition of sub-study analysis population • switched names of relevant and evaluable cycles • reduced number AE tables for ITT population • dropped nonparametric analysis for Likert pain score in the sub-study
2.0	17NOV2017	Incorporate protocol version 2.0
3.0	25JUNE2018	Incorporate protocol version 3.0; remove the randomized arm; add 7-day lockout for diary entries, follow-up for 6 weeks post-delivery for any on-treatment pregnancies, added serum pregnancy test for all suspected pregnancies

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AESI	adverse event of special interest
BMI	body mass index
CRF	case report form
DSMB	data and safety monitoring board
eCRF	electronic case report form
ECYC	evaluable for cycle control
EP	evaluable for pregnancy
ICH	International Council for Harmonization
ITT	intent to treat
IUD	intrauterine device
MedDRA	Medical Dictionary for Regulatory Activities
PID	pelvic inflammatory disease
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment-emergent adverse event
US	United States

1 INTRODUCTION

This document presents the planned statistical analyses for Sebela Pharmaceuticals Development LLC (Sebela) study titled "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, version 3.0, dated June 15, 2018. The statistical analysis plan (SAP) summarizes key aspects of the study rationale and design to provide context for the statistical methods. It also presents details of the planned statistical methods addressing the study aims. The statistical principles applied in the design and planned analyses of this study are consistent with the International Council for Harmonization (ICH) guidelines E9 (Statistical Principles for Clinical Trials).

Sebela or its designee, will write the clinical study report (CSR) following the guidelines in the ICH E3 document.

1.1 Background of VeraCept

The VeraCept Intrauterine Contraceptive ("VeraCept") is designed as a hormone free, low dose, copper-releasing birth control method. In the United States, 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 [1].

Contraceptive options for the 38 million US women using contraception include permanent sterilization (tubal ligation or vasectomy in male partner), contraceptive implants, intrauterine devices (IUDs), 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 [2]. The CHOICE Study showed that the pill failure rate is 20 times higher than the failure rate with IUDs [3,4].

Intrauterine devices have high initial costs, and therefore early discontinuation rates have a 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 IUD 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 IUDs in most studies range from 4%-15% [5,6,7].

With high unintended pregnancy rates in the United States (49%) [1], additional effective, safe, and long-acting reversible contraceptives are needed. An IUD 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.

The favorable safety, tolerability, and effectiveness data observed at 24-months in the Phase 2 study support initiation of this Phase 3 clinical trial for VeraCept.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 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

2.2 Endpoints

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 include:

Contraceptive efficacy

- Pearl Index at Years 4 and 5 as well as cumulatively through Years 4 and 5
- Pregnancy percentage by life table analysis (Kaplan Meier) at Years 1, 2, 3, 4, and 5

Study drug placement

- Ease of 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, and 5

Tolerability

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

- Reasons for discontinuation

Return to fertility

- Pregnancy rate in subjects who wish to become pregnant after 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.

3 STUDY DESIGN AND INVESTIGATIONAL PLAN

This study is a prospective, multi-center, single-arm, open-label, Phase 3 clinical study to 3 years with an extension up to 5 years.

3.1 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.

3.2 Study Duration

Subject enrollment will take approximately 9 months. Subjects will be followed for up to 5 years after VeraCept placement. Women requesting VeraCept removal for a desired pregnancy will be followed for up to 1 year after the IUD is removed. The total study duration for a subject being followed for return to fertility could be up to 6 years. Any on-treatment pregnancies will be followed through delivery and for at least 6 weeks post-delivery.

3.3 Number of Subjects

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

3.4 Investigational Sites

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

3.5 Follow-up

Subjects will have physical assessments (office visits) at Weeks 6, 13, 26, and 52 in Year 1, and then every 6 months for up to 5 years after VeraCept placement. Regular follow-up contact visits will be conducted monthly starting at Week 17, except when there is a scheduled office visit, through Year 3. For Years 3 to 5, additional visits will be conducted if necessary for safety issues.

Follow-up after early study drug removal:

All subjects who have the IUD removed while on the study, for any reason, will be required to use an alternative contraceptive for the first 2 weeks following removal. Hormonal contraceptive pills and emergency contraception will be reimbursed by the sponsor as a contraceptive option during this time unless the subject has a medical condition precluding their use.

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 will be followed through delivery and for at least 6 weeks post-delivery. Any infant abnormalities should be reported.

3.6 Study Schedule of Assessments

A schedule of assessments is provided in Table 1.

3.7 Determination of Sample Size

Approximately 1,605 subjects will be enrolled into this study to receive VeraCept on an open-label basis. It is planned that 1,480 of the 1,605 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 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 that 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% CI 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.

3.8 Interim Analyses

The Sponsor may review the primary and secondary endpoints for the study 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.

3.9 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% CI of the cumulative pregnancy percentage (Kaplan-Meier) at the given time point (e.g., Cycle 6) for the VeraCept treatment. If the lower bound of the 95% CI 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 time point of interest (e.g., Cycle 6) for the DSMB meeting. The time point 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.

4 STATISTICAL METHODOLOGY AND ANALYSIS

4.1 Definitions and Derivations

4.1.1 Standard Calculations

Variable	Calculation
Age (Years) at Informed Consent	Floor [Date of informed consent – date of birth+1) /365.25]
Height	Height entries made in inches (in) are converted to centimeters (cm) using the following formula: height (cm) = height (in) * 2.54
Weight	Weight entries made in pounds (lb) are converted to kilograms (kg) using the following formula: weight (kg) = weight (lb) / 2.2046
Temperature	Temperature entries in degrees Fahrenheit are converted to degrees centigrade using the following formula: temp (degrees centigrade) = 5/9 * [temp (degrees Fahrenheit) - 32]
Body Mass Index (BMI)	BMI is calculated using height (cm) and weight (kg) using the following formula: BMI (kg/m^2) = weight (kg) / [[height (cm)/100]^2]

4.1.2 Reference Date and Study Day Calculation

A subject could have 2 study drug insertion attempts, which could be on different dates. The following 2 study reference dates will be defined to meet the analysis requirement specified in the protocol and this SAP.

- First study reference date=date of the first insertion attempt
- Second study reference date=date of successful insertion

The first study reference date will be used for Intent-to-Treat (ITT) analysis to include all data since first device insertion attempt regardless of insertion success or failure (e.g., AEs related to replacement procedure).

The second study reference date will be used to define exposure period and analysis visit windows for all cycle-based analysis and analysis for data with scheduled data collection.

The second study reference date is Day 1 of Cycle 1.

For both reference dates, study day will be calculated as follows:

If event date ≥ study reference date:

Study day of event = Event date – Study reference date + 1

If event date < study reference date:

Study day of event = Event date – Study reference date

4.1.3 Baseline and Change from Baseline

Baseline is defined as last non-missing observation before or on date of successful insertion

- Change from baseline (CHG)= post-baseline value – baseline
- Percent change from baseline =100.0×CHG/Baseline

4.1.4 Analysis Windows

For analysis purpose, early termination visits and unscheduled follow-up visits will be assigned analysis visits according to the analysis windows in the following table. This mapping applies to labs, vital signs, and all other data planned to be collected and analyzed by visit in the SDTM finding domains. Where multiple measurements for a particular parameter appear within an analysis window the result closest to target day will be used. If equidistant, the later result will be used for the summary measure. Though all measures may not be used in the data summaries (e.g., 2 lab measures within the same analysis visit window), all measurements appear in the datasets and listings.

Analysis windows:

Scheduled Visit (Subject Visit Window)	Analysis Visit	Analysis Window Target Day	Analysis Window	
			Lower Bound	Upper Bound
Visit 1/Screening				
Visit 2 (Day 1)	Baseline	1		1
Visit 3 (Week 6±1 week)	Week 6	42	2	67
Visit 4 (Week 13±2 weeks)	Week 13	91	68	137
Visit 5 (Week 26±2 weeks)	Week 26	182	138	273
Visit 6 (Week 52±2 weeks)	Week 52	364	274	456
Visit 8 (Month 18± 1 month)	Month 18	548	457	639
Visit 9 (Month 24± 1 month)	Month 24	730	640	822
Visit 10 (Month 30± 1 month)	Month 30	913	823	1004
Visit 12 (Month 36± 1 month)	Month 36	1095	1005	1187
Visit 13 (Month 42± 1 month)	Month 42	1278	1188	1369
Visit 14 (Month 48± 1 month)	Month 48	1460	1370	1551
Visit 15 (Month 54± 1 month)	Month 54	1643	1552	1734
Visit 16 (Month 60± 1 month)	Month 60	1825	1735	≥1735

4.1.5 Exposure Periods

The first exposure cycle starts on Day 1 of successful study drug insertion. A full exposure cycle is comprised of 28 days. One woman-year comprises thirteen 28-day cycles. The following exposure periods are defined for analysis in terms of planned study days and study cycles to facilitate the efficacy and certain safety analyses.

Exposure Period	Study Day of Period Start (PSTDY)	Study Day of Period End (PENDY)
Year 1 (Cycle 1- Cycle 13)	1	364
Year 2 (Cycle 14-Cycle 26)	365	728
Year 3 (Cycle 27-Cycle 39)	729	1092
Year 4 (Cycle 40-Cycle 52)	1093	1456
Year 5 (Cycle 53-Cycle 65)	1457	1820
First 2 Years (Cycle 1-Cycle 26)	1	728
First 3 Years (Cycle 1-Cycle 39)	1	1092
First 4 Years (Cycle 1-Cycle 52)	1	1456
5 Years (Cycle 1-Cycle 65)	1	1820

Type of Events and Study Day During an Exposure Period

ETYPE	Event	Study Day of Event (EVTDY)
A	Expulsion	Study Day of Expulsion date
B	Expulsion followed by conception within 7 days	Study Day of Expulsion date
C	Removal	Study Day of Removal date
D	Removal followed by conception within 7 days	Study Day of Removal date
E	Pregnancy before expulsion	Study Day of Conception date
F	Pregnancy before removal	Study Day of Conception date
H	Lost to follow-up without pregnancy, expulsion or removal	Study Day of Last Date Device in Situ.
I	Complete period without pregnancy, expulsion or removal	Study Day of Period End Date

Note: Removal due to partial expulsion will be treated as expulsion

Exposure Duration in Days (EXDUR):

if EVTDY-PSTDY>0 then EXDUR = min(EVTDY-PSTDY+1, PENDY-PSTDY+1);

else EXDUR=.;

Exposure Duration in Cycles (NCYCF) = EXDUR/28

Number of Completed Cycles (NCYCC) = INT(NCYCF)

Number Relevant Cycles (NCYCR)

=NCYCC+1 if last partial cycle is >=23 days

=NCYCC+1 if last partial cycle ETYPE is B or D or E or F

=NCYCC, otherwise.

Number of Cycles with back-up contraceptives (including emergency contraception) or no intercourse within the period or there is no diary data (NCYCEXCL):

Exclude from NCYCEXCL the cycle in which the subject had an on-treatment pregnancy (ETYPE is B, D, E, F).

Back-up contraceptives or intercourse history are recorded in subject's diary.

If there are missing values then they will be handled as follows:

Missing back-up contraceptive diary entries will be treated as no back-up contraceptive use.

Missing intercourse diary will be treated as no intercourse.

Number of Evaluable Cycles (NCYCEV) =NCYCR-NCYCEXCL

For cumulative time periods, calculate cycle number of event:

Cycle Number of Event (CYCLEN) =CEIL(NCYCF)

Cycle Number of Event after Compression (CYCLENAC)= CYCLEN-NCYCEXCL

4.1.6 Pearl Index

Pearl Index is defined as the number of on-treatment pregnancies per 100 women years. On-treatment pregnancy is defined as the estimated conception date being on or after the insertion date (must be a successful insertion) and no more than 7 days after the study drug is removed or expelled. One women year is defined as comprising thirteen 28-day cycles.

Point estimate of Pearl Index: $x \times \frac{1300}{E}$

where x is the number of on-treatment pregnancies and E is the number of 28-day evaluable exposure cycles

Cycles during which no intercourse occurs or backup methods of contraception (including emergency contraception) are used or there is no diary data 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 study drug placement relative to the subject's last pre-insertion menses.

If ETYPE is B or D or E or F, then PREGNANCY = 1; else PREGNANCY = 0

x = sum of PREGNANCY

E = Number of Evaluable Cycles (NCYCEV)

4.1.7 On-Treatment Pregnancy Rate

On-Treatment Pregnancy Rate is defined as cumulative probability of on-treatment pregnancy at the end of each analysis interval. It is calculated as failure probability from a survival analysis.

Time variable:

CYCLENAC= Time to conception in cycles (compressed)

CYCLEN = Time to conception in cycles (uncompressed)

Event variable PREGNANCY as defined above.

4.1.8 Study Drug Expulsion Rate

The expulsion rate is defined as cumulative probability of device expulsion at the end of an exposure period. It is calculated as failure probability from a survival analysis.

Time variable

CYCLEN= Time to expulsion in cycles (uncompressed)

Event variable Expulsion

If ETYPE is A or B, then EXPULSION=1; else EXPULSION=0

Expulsion includes removal due to partial expulsion

4.1.9 Continuation Rate

Continuation rate is defined as the cumulative probability of study drug use at the end of a study period. It is calculated as survival probability from a survival analysis.

Time variable:

CYCLEN= Time to study drug discontinuation in cycles (uncompressed)

Event Variable DISCONTINUATION:

If ETYPE is A or B or C or D then DISCONTINUATION=1;

else DISCONTINUATION=0

Those lost to follow-up and became pregnant before removal or expulsion are censored.

4.1.10 Adverse Event

4.1.10.1 Definition of an Adverse Event

An AE 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.

The analysis of AEs will be based on the principle of treatment emergence. Treatment-emergent AEs (TEAEs) will be defined as events that occur (or worsen) on or after the first treatment date of the study drug

In this study, Pregnancy is an outcome, and not an AE.

4.1.10.2 Definition of a Serious Adverse Event

A serious adverse event (SAE) is any AE 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.

4.1.10.3 Adverse Events of Specific Interest

Adverse events of particular clinical importance, other than SAEs will be classified as AEs of specific interest (AESIs). For this study, AESIs refer to reports of insertion pain assessed immediately after insertion, pelvic infection (PID or endometritis), 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.

4.1.10.4 Adverse Event Relationship to Study Treatment

The relationship of an AE to the drug will be assigned as one of following relationships:

Not related, unlikely related, possibly related, probably related, and related.

For analysis purposes, “possibly related,” “probably related,” and “related” to an investigational medical product are considered adverse reactions and will be reported as "Related."

“Unlikely” and “not related” do not qualify as a causal relationship and will be reported as “unrelated”.

A missing relationship will be imputed as “related”.

4.1.10.5 Adverse Events Related to Study Procedures

Adverse events that occur during the study drug placement procedure or removal procedure will be reported on the AE electronic case report form (eCRF) with a causality assessment of “related to study drug placement procedure.”

A missing relationship will be imputed as “related to study drug placement procedure.”

4.1.10.6 Adverse Event Severity

The investigator will assess the severity of the AE and severity is one of the following 4 values: Mild, Moderate, Severe, or Life-threatening.

For analysis purpose, Life-threatening will be coded as severe; missing severity will be imputed as severe.

4.1.11 Imputing Missing or Incomplete Dates of Adverse Events and Concomitant Medications

The most conservative approach will be systematically considered. If the AE onset date is missing / incomplete, it is assumed to have occurred during the study treatment phase (i.e., considered a TEAE) except if the partial onset date or other data such as the stop date indicates differently. Similarly, a medication with partial start and stop dates could be considered as both a prior and concomitant treatment.

The following algorithms will be applied to missing and incomplete start and stop dates:

Start Dates

- If the day portion of the start date is missing, then the start date will be estimated to be equal to the date of first insertion, provided the start month and year are the same as the first insertion and the stop date is either after the first insertion or completely missing. Otherwise, the missing day portion will be estimated as "01."
- If both the day and month portions of the start date are missing, then the start date will be estimated to be equal to the date of first insertion, provided the start year is the same as the first insertion and the stop date is either after the first insertion or completely missing. Otherwise, the event will be assumed to start on the first day of the given year (e.g., ??-???-2013 is estimated as 01-JAN-2013).
- If the start date is completely missing and the stop date is either after the first insertion or completely missing, the start date will be estimated to be the day of first insertion. Otherwise, the start date will be estimated to be the first day of the same year as the stop date. All other non-AE and non-concomitant medication day calculations where only partial dates are available will be handled as follows: the first day of the month will be used in the calculations if the day part of a start date is missing while January 1 will be employed if both the month and day parts of a start date are missing.

Stop Dates

- If only the day of resolution is unknown, the day will be assumed to be the last of the month (e.g., ??-JAN-2013 will be treated as 31-JAN-2013).
- If both the day and month of resolution are unknown, the event will be assumed to have ceased on the last day of the year (e.g., ??-???-2013 will be treated as 31-DEC-2013).
- If the stop date is completely missing or the event is continuing, the event will be assumed to be after first insertion and will be imputed using the last known date on the study.

4.2 Analysis Populations

4.2.1 Analysis Populations

- **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 as follows. 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

  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 the Sebela and its designee.

- **Evaluable for Cycle Control (ECYC):**

  ITT 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.

4.3 Analysis Population Subgroups

The following subgroups will be analyzed separately.

BMI group at enrollment:

- <30 kg/m^2
- ≥ 30 kg/m^2

Race group:

- White
- Non-white

Parity status at enrollment:

- Parous - having given birth 1 or more times
- Nulliparous - having never borne children

Age at Enrollment:

- ≤ 35 years old
- 36-45 years old

4.4 General Data Presentation Plan

Analyses will be conducted using SAS® software, Version 9.4 or above (SAS Institute Inc, Cary, NC).

Analyses will be conducted using the initial 3-year data to support submission for VeraCept approval, and data will be reanalyzed at the end of the 5-year follow-up. Unless otherwise specified, the table summary for the main study will display columns as follows:

Analysis Population	**Table Display Columns**		
ITT	Age (years) ≤ 35	Age (years) 36-45	Overall
Safety	Age (years) ≤ 35	Age (years) 36-45	Overall
EP	Age (years) ≤ 35		
ECYC	Age (years) ≤ 35	Age (years) 36-45	Overall

Other subgroup analyses (race group, BMI group at enrollment, parity at enrollment) will be conducted for all subjects in the corresponding population without further sub-setting by other subgroup variables.

In general, all efficacy and safety variables will be summarized using descriptive statistics and graphs as appropriate. Continuous variables will be summarized by descriptive statistics (sample size (n), mean, SD, minimum, median, and maximum). Categorical variables will be summarized

in frequency tables (frequencies and percentages). Time to event variables will be summarized by Kaplan-Meier method. Individual data will be presented in subject listings.

Means and medians will be displayed with 1 more decimal place than the collected data, and SDs will have 1 more decimal place than the means and medians. Minimum and maximum will be displayed with the same number of decimal places as the collected data. Percentages will be rounded to 1 decimal place.

No formal statistical testing will be performed on demographic, baseline characteristic, and safety data unless stated otherwise for a specific parameter in the SAP. For efficacy variables, all statistical tests will be conducted at a 2-sided significance level of 5% unless otherwise specified. Where appropriate, point estimates, together with their 95% CIs, will be presented.

Only observed data, with no data imputation, will be used for the efficacy analyses unless otherwise specified. Safety analyses will also be conducted on the observed data. However, for the start date/time of an AE or medication being partially or completely missing, the worst-case scenario will be applied. That is, the AE will be assumed to be treatment emergent, and the medication will be considered concomitant.

4.5 Disposition of Subjects

Disposition of subjects will be summarized for the ITT population.

For the initial 3-year study participation:

A disposition table will report the following:

- The number and percentage of subjects who were enrolled, completed Year 1 (first 13 cycles), and discontinued the study during Year 1 with reason for discontinuation
- The number and percentage of subjects who entered Year 2 (second 13 cycles), completed Year 2, and discontinued the study during Year 2 with reason for discontinuation
- The number and percentage of subjects who entered Year 3 (third 13 cycles), completed Year 3, and discontinued the study during Year 3 with reason for discontinuation
- The number and percentage of subjects who were enrolled, completed 3 years, and discontinued the study during the 3 years with reason for discontinuation
- The number and percentage of subjects in each analysis population

A Kaplan-Meier plot will be used for the number of cycles from the date of successful VeraCept placement to study discontinuation.

- The table summary and Kaplan-Meier figure will be repeated by parity at enrollment
- Table summary will further be repeated for each clinical site

Listings will be generated for the following:

- Subject's membership in each analysis population and reason for exclusion from each analysis population
- Subjects with inclusion/exclusion criteria violations and waivers

Five-year participation:

At the end of the 5-year study, a summary of subject disposition for Year 4 (the fourth 13 cycles) and Year 5 (the fifth 13 cycles), separately, and for 5 years cumulatively will be added to the above 3-year disposition table. Kaplan-Meier plots will be created using 5-year disposition data.

4.6 Protocol Deviations

Number (%) of subjects with protocol deviations will be summarized by category (major/minor) and deviation type for the ITT population. The detail about each protocol deviation will be presented in the protocol deviation listing.

4.7 Baseline Demographics and Characteristics

Baseline demographics will be summarized for the ITT, EP, Safety, and ECYC populations. All other baseline characteristic information will be summarized for the ITT population only.

4.7.1 Baseline Demographics

The following variables collected at Screening/Baseline will be included in the baseline demographics summary table:

- Ethnicity
- Race
- Age (years) at enrollment
- Height (cm) at enrollment
- Weight (kg) at enrollment
- BMI (kg/m^2) at enrollment
- BMI group (<30 kg/m^2, ≥ 30 kg/m^2) at enrollment
- Marital status at enrollment
- Parity at enrollment
- Uterine depth

All demographic and baseline characteristics will be presented in data listings.

4.7.2 Medical/Surgical History

Number (%) of subjects reporting Medical /Surgical history will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) primary system organ class (SOC) and preferred term (PT).

An additional summary will be provided for Medical/Surgical history recorded as ongoing.

Medical/Surgical History will be presented in a data listing.

4.7.3 Baseline Physical Examination

Physical examination by body system (General appearance, Skin, Head, eyes, ears, nose and throat, Thyroid, Lungs, Back, Breasts, Heart, Abdomen, Extremities, Neurological) will be summarized by age group and overall.

4.7.4 Gynecological History

Gynecological history data will be summarized for all questions collected on the case report form (CRF).

All gynecological history will be presented in a data listing.

4.7.5 Menstrual History

Menstrual history data will be summarized for all questions collected on the CRF.

All menstrual history will be presented in a data listing.

4.7.6 Cervical Cytology

Cervical cytology test results will be summarized in table and presented in a data listing.

4.7.7 Prior and Concomitant Medications

Prior and concomitant medications include any medications taken by subjects from 30 days prior to the signing of the informed consent through the end of study participation will be recorded on CRF page and coded using the WHODrug dictionary. The CSR will include the version number of the WHODrug dictionary. Prior medications are defined as those taken by the subject prior to the study drug placement. Concomitant medications are defined as those taken by the subject from the date of the study drug placement to study completion/discontinuation.

In cases where it is not possible to define a medication as prior or concomitant, the medication will be classified as concomitant.

The number (%) of subjects taking prior and concomitant medications will be summarized, separately, by ATC Level 4 and generic term for the ITT population.

All prior and concomitant medications will be presented in a data listing.

4.8 Extent of Exposure

Following parameters will be summarized for the Safety and EP populations, and summarized by parity at enrollment for the Safety and EP populations:

- Number of exposure cycles including partial cycles
- Number of complete exposure cycles
- Number of relevant cycles
- Number of cycles with back-up contraception or no intercourse
- Number of evaluable cycles for Pearl Index Calculation
- Exposure in woman years

- Exposure in woman years calculated from complete cycles
- Exposure in woman years calculated from relevant cycles
- Exposure in woman years calculated from evaluable cycles

4.9 Primary Endpoint Analysis

The primary efficacy endpoint is contraceptive efficacy through 3 years of use and will be analyzed using the Pearl Index with a 95% CI (CI) for women in the EP population.

The Pearl Index is defined as the number of on-treatment pregnancies per 100 women years. On-treatment pregnancy is defined as the estimated conception date being after the insertion date and no more than 7 days after the VeraCept is removed or expelled. One woman year is defined as comprising thirteen 28-day cycles.

Point estimate of Pearl Index: $x \times \frac{1300}{E}$

95% CI: $\left(\frac{1}{2}\chi^2_{(0.025,2x)} \times \frac{1300}{E}, \frac{1}{2}\chi^2_{(0.975,2(x+1))} \times \frac{1300}{E}\right)$

where x is the number of on-treatment pregnancies and E is the number of 28-day evaluable exposure cycles and $\chi^2_{(p,df)}$ is the pth quantile of χ^2-distribution with df degrees of freedom.

Cycles during which no intercourse occurs or backup methods of contraception (including emergency contraception) are used or there is no diary data 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 relative to the subject's last pre-insertion menses.

x =sum of PREGNANCY

E =number of Evaluable Cycles (NCYCEV)

Pearl Index point estimate and 95% CI will be calculated for Year 1, Year 2, and Year 3, separately, and for 3 years cumulatively.

The analysis will be repeated for the following subgroups

- Race (white, non-white)
- BMI group at enrollment
- Age group at enrollment
- Parity at enrollment

4.10 Secondary Endpoint Analysis

All secondary endpoint analyses will be descriptive.

4.10.1 Contraceptive Efficacy

The Pearl Index and 95% CI will be calculated for Years 4 and 5, as well as cumulatively through Years 4 and 5. The calculation will follow the same rules used for the primary analysis for the initial 3 years.

Time to on-treatment pregnancy from the date of successful insertion will be analyzed via Kaplan-Meier method for the EP population. Cumulative probability of on-treatment pregnancy (contraceptive failure rate) at the end of Years 1 through 5 will be estimated. The complementary log-log transformation will be used to construct 95% CIs. The estimated pregnancy probability and confidence bound via Kaplan-Meier method multiplied by 100 is expected to be comparable to the Pearl Index point estimate and confidence bound via Poisson distribution to provide supportive evidence of contraceptive efficacy.

As with the primary endpoint analysis, cycles during which no intercourse occurs or backup methods of contraception (including emergency contraception) are used will be excluded from the analysis unless the subject had an on-treatment pregnancy in that cycle. The remaining cycles will be compressed to provide contiguous cycles for the time-to-event analysis. This analysis will use the time-to-event and censor variables (CYCLENAC and PREGNANCY) defined in the exposure section.

A sensitivity analysis will be performed without excluding those cycles with backup contraception or no intercourse. The sensitivity analysis will use the time-to-event and censor variables (CYCLEN and PREGNANCY) defined in the exposure section.

Life-table analysis via Kaplan-Meier method will be repeated for the following subgroups:

- Race (white, non-white)
- BMI group at enrollment
- Age group at enrollment
- Parity at enrollment

4.10.2 Study Drug Placement

Study drug placement data will be summarized for the ITT and Safety populations while study drug removal data will be summarized for the Safety population only. The study drug placement and removal data will be presented in the listings.

4.10.2.1 Study Drug Placement

The following parameters will be reported in the table for study drug placement:

Number (%) of subjects who

- Attempted first insertion
    - Had successful first insertion
    - Failed first insertion
- Attempted second insertion after failed first insertion
    - Had successful second insertion
    - Failed second insertion

Total number of insertions

- Number of failed insertions

    - Number (%) of failed insertions by reason of failure
- Number (%) of insertions with local anesthesia
- Number (%) of insertions required cervical dilation
- Insertion ease and pain
    - Frequency distribution of insertion ease as assessed by investigator
    - Frequency distribution of insertion pain assessed immediately after insertion as reported by subject
    - Frequency distribution of insertion pain assessed immediately after insertion will also be summarized for subjects with prophylactic pain medication prior to insertion as well as for subjects without prophylactic pain medication prior to insertion.

4.10.2.2 Study Drug Removal

The following parameters will be reported in the table for the initial three years' follow-up and at the end of the 5-year study.

Number (%) of subjects who had study drug removal

- Frequency distribution of removal ease as assessed by investigator
- Frequency distribution of removal pain as reported by subject

4.11 Multiplicity Adjustment

There is no planned interim to stop the trial before the end of 3 years to claim contraceptive efficacy. There is no need for multiplicity adjustment for type I error α.

4.12 Safety and Tolerability

Adverse events will be coded and classified by SOC and PT using MedDRA. The summaries of AEs will be limited to TEAEs. Number (%) of subjects reporting AEs and SAEs will be summarized for the Safety population. A few selected AE and SAE tables will also be summarized for the ITT population.

4.12.1 Brief Summary of Adverse Events

The number (%) of subjects reporting any of the following events during study will be reported in the brief summary of AEs for the ITT and Safety populations:

- AE
- AE related to study drug use
- AE related to study drug placement/removal procedure
- SAE
- SAE related to study drug use
- SAE related to study drug placement/removal procedure

- AE leading to study drug removal
- AE leading to study discontinuation
- Death

4.12.2 Adverse Events by System Organ Class and Preferred Term

The incidence of AEs and SAE will be summarized by MedDRA primary SOC and PT. The summary will include the total number and percentage of subjects reporting an AE within an SOC and/or PT.

The incidence of AEs by SOC and PT for the Safety and ITT populations

The incidence of AEs by SOC and PT by maximum severity for the Safety population

The incidence of AEs by SOC and PT by closest relationship to study drug use for the Safety population

The incidence of AEs by SOC and PT by closest relationship to drug placement/removal procedure for the Safety and ITT populations

The incidence of SAEs by SOC and PT for the Safety and ITT populations

The incidence of SAEs by SOC and PT by maximum severity for the Safety population

The incidence of SAEs by SOC and PT by closest relationship to study drug use for the Safety population

The incidence of SAEs by SOC and PT by closest relationship to drug placement/removal procedure for the Safety and ITT populations

The incidence of AE leading to study drug removal by SOC and PT for the Safety population

The incidence of AE leading to study discontinuation by SOC and PT for the Safety population

Listing of AE leading to death for the ITT population

Incidence of AEs experienced by at least 5% of subjects by SOC and PT for the Safety population

Incidence of AESIs(e.g. pain during insertion, pelvic inflammatory disease, ectopic pregnancies, uterine perforations, expulsions, uterine perforation, dysmenorrhea, and abdominal pain) will be summarized for Safety and ITT populations.

4.12.3 Narratives of Deaths, Serious Adverse Events, and Other Significant Adverse Events

Narratives of deaths, SAEs, and other significant AEs will be provided in the relevant section of the clinical study report.

4.12.4 Adverse Event Listing

A complete subject listing of all AEs will be provided in Appendix 16.2 to the study report. This listing will include treatment, AE verbatim term, MedDRA primary SOC and PT, the time of onset and cessation of the event relative to the first insertion of study drug, duration of the AE, whether serious or not, severity, relationship to study drug, action taken, and outcome. Treatment-emergent and non-treatment-emergent events will be listed separately.

In addition, separate listings of all SAEs, AEs related to study drug, AEs related to study drug placement/removal procedure, AEs leading to death, AEs leading to study drug removal, and AEs as primary reason for exiting study will be provided.

4.12.5 Subgroup Analysis for Adverse Events

Tables of brief summary of AEs, AEs by SOC and PT, SAEs by SOC and PT, and AESIs will be presented by the following subgroup variables for the Safety population:

- Race group
- BMI group at enrollment
- Age group at enrollment
- Parity status at enrollment

4.12.6 Bleeding and Spotting Patterns

Bleeding and spotting patterns will be summarized (per Mishell [8]) for the ECYC population for the first year of treatment by the number of days (n, mean (SD), min, median, max) in each 28-day cycle with bleeding or spotting, bleeding only, and spotting only. Number (%) of subjects with amenorrhea (absence of menstruation) will also be reported by cycle. The analysis will be repeated by parity at enrollment.

Occurrence and intensity of vaginal bleeding and spotting will be recorded daily by subjects in e-diary. If there are more than 7 missing values in a cycle of 28 days, the cycle will not be used for this analysis. Single missing values will be imputed as the maximum bleeding intensity recorded on the day before and after the missing day. Last value of the previous cycle and the first value of the next cycle could be used for imputation for the single missing value in the current cycle. Two consecutive missing values will be imputed by carrying forward the last non-missing and carrying backward the next non-missing. Three or more consecutive missing will be left missing.

4.12.7 Subject Discomfort with Study Drug

The occurrence and severity of menstrual pain or cramping will be summarized by cycle for the ECYC population for the first year of treatment.

Only cycles with assessment of bleeding (menstruation) will be included in the analysis.

The analysis will be repeated by parity status at enrollment.

Experience of any menstrual pain or cramping will be recorded daily by the subject in the e-diary in the first year. If menstruation reported is in a cycle, but menstrual pain or cramping is completely missing, then missing values will be imputed as pain or cramping of the maximum intensity.

The following parameters will be reported in the table and data will be presented in the listing:

- Number (%) of subjects with menstrual pain by cycle
- Number (%) of subjects with menstrual pain by maximum severity by cycle
- Number (%) of subjects with menstrual cramping by cycle
- Number (%) of subjects with menstrual cramping by maximum severity by cycle

4.12.8 Cumulative VeraCept Continuation Rates

Cumulative VeraCept continuation rates for Years 1 through 5 will be estimated via Kaplan-Meier method for the Safety population. The complementary log-log transformation will be used to construct 95% CIs. The number and percentage of subjects with each reason for discontinuation will be summarized. The analysis will also by repeated by parity at enrollment.

Time to VeraCept discontinuation from successful insertion will be analysis variable.

- If a subject discontinued VeraCept because of desire of pregnancy, the subject will be censored at the cycle of removal.
- If a subject discontinued because of pregnancy, VeraCept should be removed. However, according to protocol, the study drug could be removed at the time of delivery. So, for consistency, the subject will be censored at the cycle of removal or conception if not removed.
- If a subject is lost to follow-up, she will be censored at the last cycle in which the study drug was known to be in place.
- If a subject completed the exposure period, the subject will also be censored at the cycle of the period end.

4.12.9 VeraCept Expulsion Rates

Cumulative VeraCept Expulsion Rates for Years 1 through 5 will be estimated via Kaplan-Meier method for the Safety population. The complementary log-log transformation will be used to construct 95% CIs. The subgroup analysis will also be repeated by parity status at enrollment.

VeraCept expulsion includes both total expulsion and partial expulsion. Total expulsion is defined as cases in which VeraCept is observed in the vagina, not shown in the uterus by ultrasound, or if the women confirmed expulsion. Partial expulsion cases are defined as when VeraCept is visible in the cervical canal by gynecologic exam or ultrasound. If partially expelled VeraCept is removed, the removal will be considered an expulsion event for this analysis.

- Time to expulsion in cycles will be defined as time to total expulsion discovered or removal of the partially expelled VeraCept from the date of successful insertion
- Removal of VeraCept for any other reason will be censored at the removal cycle.
- If a subject discontinued because of pregnancy, the subject will be censored at the cycle of conception
- Lost-to-follow-up will be censored at the last cycle where VeraCept is in Situ.
- Those with VeraCept still in place for protection at the end of exposure period will be censored at the end of exposure period.

4.12.10 Return to Fertility

Subjects in the safety set 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 number (%) of subjects with return to fertility response will be summarized follows:

- Number of subjects who desire pregnancy after having VeraCept removed
- Number of subjects successfully contacted (b)
- Number of subjects successfully contacted but go on to use other birth control (c)
- Number of pregnancies (x)
- Pregnancy rate at the end of 1-year follow-up (%) = $100 \times \frac{x}{b-c}$

The pregnancy rate will also be calculated by parity, and by duration of use (presented by year where year = thirteen 28-day cycles) of VeraCept removal if there are more than 30 subjects at risk (b-c) in each year.

4.12.11 Vital Signs and Weight

The observed values and changes from baseline in the following vital signs and weight parameters will be summarized by visit for the Safety population:

- Systolic blood pressure (mm Hg)
- Diastolic blood pressure (mm Hg)

- Pulse rate (bpm) sitting
- Respiration rate (breaths/min)
- Body temperature
- Body weight (kg)

The number and percentage of patients reporting potentially clinically meaningful observations as defined below will be summarized by visit and treatment group:

- Systolic blood pressure: ≤ 80 mm Hg or ≥ 140 mm Hg
- Diastolic blood pressure: ≤ 40 mm Hg or ≥ 90 mm Hg
- Pulse rate: ≤ 50 bpm or ≥ 100 bpm
- Respiration rate: < 8 or > 20 breaths/min

Vital signs and weight will be included in data listings.

4.12.12 Physical Examination

Physical examination includes examination of general appearance; skin; head, eyes, ears, nose and throat; thyroid; lungs; back; breasts; heart; abdomen; extremities; and neurological system.

The number (%) of subjects with treatment-emergent abnormal (not clinically significant) and clinically significant abnormal results will be tabulated by body system by visit for the Safety population.

Physical examination results will be included in data listings.

4.12.13 Laboratory Results

All laboratory data will be presented in the listings.

5 REFERENCES

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7. Hubacher D, et al., Preventing copper intrauterine device removals due to side effects among first-time users: randomized trial to study the effect of prophylactic ibuprofen. Human Reproduction, 2006. 21(6): p. 1467-1472.

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Table 1: Study Schedule of Assessments

		Screen	Years 1-5					Other
		Screening	**Enrollment (VeraCept Placement) Day 1**	**Office Visits: W 6 ± 1 w W 13 ± 1w W 26 ± 2w W 52 ± 2w**	**Regular Contact[10]: 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 (± 1 m)**	**Mth 60 ± 1 m or Exit Visit**	**Monthly Contact to confirm pregnancy for those desiring pregnancy[8]**
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 IUD 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	
Other	Contact IWRS	X[13]	X[14]				X	
	Measure Uterine Depth		X[9]					
	IUD placement		X[9]					
	IUD placement ease		X					
	IUD placement pain (11-point scale)		X[11]					
	IUD removal						X	
	IUD removal ease						X	
	IUD removal pain (11-point scale)						X[12]	
	Concomitant contraception		X	X	X	X	X	
	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]

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 IUD 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 60 or exit visit and 17 days after removal/study exit by the subject at home, with a follow up call by the study coordinator or PI required to document the results.

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 retest should be done 3-months post-treatment to confirm cure.

6. Subjects will complete an e-diary through Month 60 and will receive detailed instructions on how to complete the daily e-diary. From Month 13 – Month 60, only other contraceptive use and intercourse 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. via phone, email, etc.) and documented in the source document and eCRF.

9. Obtain uterine depth measurement prior to insertion

10. Contact subject (e.g. via phone, email, etc). Starting at Week 17 from day of VeraCept insertion.

11. See protocol Appendix 2 for the IUD Insertion Subject Numeric Pain Rating Scale

12. See protocol Appendix 3 for the IUD Removal Subject Numeric Pain Rating Scale

13. 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

14. Contact the IWRS to obtain an enrollment number, the IUD dispensation assignment, and initiate the enrollment diary. If an IUD insertion is a failure, contact the IWRS to record the IUD insertion failure and to obtain a second IUD dispensation assignment or to discontinue the subject.