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Document
Statistical Analysis Plan

Study Title
Evaluation of the Effectiveness, Feasibility, Safety and Tolerability of the ContraMed VeraCept Intrauterine Copper Contraceptive for Long Acting Reversible Contraception

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Notes
This SAP is being submitted to ClinicalTrials.gov in compliance with the Final Rule for clinical trial results information reporting.

Protocol CMDOC-0008

Evaluation of the Effectiveness, Feasibility, Safety and Tolerability of the ContraMed VeraCept Intrauterine Copper Contraceptive for Long Acting Reversible Contraception

Statistical Analysis Plan

Prepared for:

Sebela Pharmaceuticals Development LLC

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Note: The original Sponsor ContraMed, LLC [redacted] on June 1, 2018.
Sebela Pharmaceuticals Development LLC is now the Sponsor of CMDOC-0008

STATISTICAL ANALYSIS PLAN APPROVAL

RESPONSIBILITY	NAME & COMPANY	SIGNATURE	DATE (DDMMMYYYY)
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LIST OF ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
EC	Emergency Contraception
ECYC	Evaluable for Cycle Control
EP	Evaluable for Pregnancy
HEENT	Head, Eyes, Ears, Nose and Throat
IND	Investigational New Drug
ITT	Intent-To-Treat
IUD	Intrauterine Device
LTFU	Long Term Follow up
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
WHO	World Health Organization

1.0 INTRODUCTION

This statistical analysis plan (SAP) was developed based on the Version 1.00 SAP for Year 1 data analysis, after reviewing the Sebela Pharmaceuticals Development LLC (Sebela) CMDOC-0008 study protocol (Version 5.0, dated as 29SEP2017) and electronic case report forms (eCRFs, dated as 30JAN2018), but before final analysis of the Year 2 and Year 3 data analysis had begun. Detailed information is given to aid in the production of the statistical outputs and the statistical section of Final Clinical Study Report (CSR). This document gives a summary of the protocol and describes the populations that will be analyzed. All subject characteristics and the efficacy and safety parameters that will be evaluated, along with the specific statistical methods, are described.

2.0 PROTOCOL SUMMARY

2.1 Background

Of all contraceptive 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. The CHOICE Study showed that the pill failure rate is 17-20 times higher than the failure rate with intrauterine devices.

Intrauterine devices have high initial costs, so early discontinuation rates have profound impacts on their cost-effectiveness. The early rates of user dissatisfaction due to complications or side effects may be associated with the materials used in these devices and/or their design. The VeraCept Intrauterine Contraceptive by Sebela is designed as a birth control device with low-dose copper trying to achieve high contraceptive effectiveness, minimal side effects and improved mechanical advantages.

2.2 Objectives

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

The purpose of the study is to obtain the safety and effectiveness data necessary to support an Investigational New Drug (IND) application to the U.S. Food and Drug Administration (FDA) for a longer term Phase III pivotal clinical study.

2.3 Trial Design

This is a prospective, multi-center, single-arm, open-label, Phase II clinical study. Each subject will be followed for 12 months after device placement for the protocol endpoints, and then every 6 months thereafter for those subjects who wish to continue study device use up to a maximum of 3 years.

Physical assessment (office visit) will occur at Weeks 6, 13, 26 and 52 after placement, with monthly telephone contact. For those subjects who wish to continue study device use after 12 months (up to 2 additional years for a total maximum of 3 years), follow-up office visits will occur every 6 months, and also contacted by phone calls, e-mail or text

message every 28 days (Cycle Contact). Additional visits will be conducted if necessary for safety issues.

2.4 Study Endpoints

2.4.1 Primary Endpoints

The primary outcome measure is study device effectiveness, evaluated as the absence of pregnancy up to 12 months (13 cycles of 28 days each) of VeraCept use.

Contraceptive failure rate will be calculated using the Pearl Index through 13 cycles. All evaluable cycles prior to discontinuation or planned removal at 12 months (13 cycles) will be included in the primary analysis of effectiveness. The calculation will be first done for all ("Total") subjects, and then for sub-groups of parous ("Parous") and nulliparous ("Nulliparous") women of child-bearing age.

2.4.2 Secondary Endpoints

The secondary endpoints concern the:

Study Device Placement

- Ease of placement
- Placement success

Subject Safety

- Serious Adverse Events
- Adverse Events

Tolerability

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

2.5 Sample Size Consideration

No formal sample size calculations were performed for this exploratory study. It is estimated that with 225 subjects enrolled with age 18-35, a 12-month (13 cycles) Pearl Index of 0.6 (1 observed pregnancy), and 2,015 evaluable cycles, we will observe a 95% confidence interval (0.1, 3.3) for the Pearl Index.

3.0 STATISTICAL METHODS

3.1 Statistical Handling Policy

3.1.1 Interim Safety Review

No formal interim analysis will be conducted, but a Medical Monitor will periodically do safety review of subject's adverse events data. If any safety concern should be identified, the Sponsor, institutional review board (IRB), and regulatory agencies, if applicable, will be informed immediately.

3.1.2 Analysis of 1-Year data

An analysis of the 1-year data was performed after all the subjects are enrolled and all the 1-year data were collected, monitored, and cleaned. All outputs in Section 5.2 that involve 1-year data were created since this analysis was the final analysis of the 1-year data. The analysis of 1-year data was the main analysis for the study. Secondarily, an analysis will be done at the end of the study to include all 3-year data.

3.1.3 Analysis Conventions

This section details general policies to be used for the statistical analyses. Departures from these general policies may be given in the specific detailed sections of this statistical analysis plan. When this situation occurs, the rules set forth in the specific section take precedence over the general policies. The following policies will be applied to all data presentations and analyses.

- Summary statistics will consist of the number and percentage of responses in each category for discrete (categorical) variables, and the number of non-missing observations (n), mean, median, standard deviation (SD), minimum, and maximum (abbreviated as 6-number summary statistics) for continuous variables.
- All mean values will be formatted to one more decimal places than the measured value, and standard deviation values will be formatted to two more decimal places than the measured value. For median values, they will be kept the same decimal place as the measured values if that is doable without losing accuracy; otherwise, they will be formatted to one more decimal place than the measured values.
- All percentages will be rounded to one decimal place. The number and percentage of categorical responses will be presented in the form XX (XX.X), where the percentage is in the parentheses. The denominator for percentage calculations will be either the number of non-missing observations (n) when this number is shown, or the total sample size of the relevant sample size for tables of adverse events, medical histories, or other tables where this number of non-missing observations (n) is not presented.
- All listings will be sorted for presentation in the order of site identifier, subject identifier, and date of procedure or event.
- When necessary for analysis purposes, partial dates will be completed (i.e., turned into complete dates) using the most conservative approach.
- All analysis and summary tables will have the population sample size in the column heading.
- Baseline is defined as the last data point before the placement of study product.
- Calculating change from baseline to a visit will be done as follows: Change from Baseline = Observed value at the visit – Baseline value.
- Subjects who have only baseline (without any post-baseline measurements) for a parameter at a visit, or only have post-baseline value for a parameter at a visit, will be excluded from the summary of change from baseline by visit for that parameter.

- Version 9.4 of SAS® or higher will be the statistical software package used to produce all summaries, listings, statistical analyses, and graphs.

3.2 Subject Disposition

Subject disposition will be summarized for the All Screened population with the following data:

- Total number of subjects who consented, enrolled and screen failures.
- The number and percentage of subjects who completed or discontinued prematurely from the study, either prior to the end of 1-year study or prior to extension study; the number and percentage of subjects who discontinued and reason for discontinuation, either 1-year or extension study, by each reason for all subjects. For those entered Extension, similar summaries will be presented for 2-year and 3-year benchmark.
- A listing of subjects who discontinued prematurely from the study, either 1-year or extension. The listing will include information about study site ID number, subject ID number, age, subject is parous or nulliparous, number of days on study, and reason for discontinuation. The number of days on study will be calculated as Device Removal Date – Device Placement Date + 1.
- The number and percentage of subjects at each scheduled visit.
- The number of subjects who were enrolled at each study site, the number and percentage of subjects who completed or discontinued either 1-year or extension, at each study site.

The End of Trial CRF will be used to determine who discontinued prematurely from the study.

3.3 Protocol Deviations

Protocol deviations will be summarized by type of deviations listed on the CRF for all ITT subjects. Both the number of deviation events and distinct number and percentage of subjects will be presented for each type of deviation.

3.4 Analysis Populations

All Screened: all subjects who signed Consent Form and screened at the study sites.

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

Safety: ITT subjects who had the device successfully placed.

Extension: ITT subjects who agreed to continue study device use after 12 months, up to 2 additional years for a total maximum of 3 years.

Evaluable for Pregnancy (EP): ITT subjects who had VeraCept placed successfully, and must meet both requirements 1 and 2 to be EP. Subjects must also meet either requirement 3 or requirement 4 to be EP.

1. between 18 to 35 years of age (inclusive) at enrollment

2. at least one report of pregnancy status after being enrolled

AND

3. have at least 1 cycle of diary with intercourse and without any backup contraception or emergency contraception (EC)

OR

4. 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.

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

A) a pregnancy did not occur; AND
B) there was an assessment of bleeding in the diary data; AND
C) the cycle has 14 or more days data.

3.5 Demographics and Pre-Treatment Characteristics

Subject demographics and pre-treatment characteristics will be summarized for the ITT analysis population, and some of these summaries may also be done for other populations when deemed important.

3.5.1 Demographics

The summary of demographics and subject characteristics will include age, race, ethnicity, education level, marital status, relationship status, how long the subject has been in her relationship, height, weight and body mass index (BMI) at baseline (from vital signs CRF), as well as uterine length (from pelvic exam CRF). The summary will be done for ITT, EP, ECYC, and include:

- The 6-number summary statistics (number of non-missing observations, mean, median, SD, minimum, and maximum) for age, height, baseline weight, baseline body mass index (BMI), and uterine length. Age will be calculated (with the INTCK function in SAS®) using the Screening Visit Date and the Date of Birth. Weight at baseline will be used for the summary.
- The number and percentage of subjects for categorical data, such as race, ethnicity, education level, parity (parous (≥1 birth) and nulliparous (not given birth)) marital status, relationship status, time (duration) of relationship, as well as the category of BMI: Underweight (< 18.5), Normal (18.5 – 24.9), Overweight (25.0 – 29.9), and Obese (≥ 30.0).

3.5.2 Medical History

Medical history data will be summarized by body system (Allergies, Heart, Digestive, Thyroid, etc.), as those reported on the CRF, for status of

- Ongoing
- Any (includes medical histories that are ongoing or resolved)

The number and percentage of subjects in each status will be provided by body system for the ITT population. If a subject reports more than one history/condition in the same body system, that subject will be counted only once for the summary of that body system.

3.5.3 Gynecological History

Gynecological history data will be summarized for the all questions collected on the CRF as follows:

- Does the subject currently use birth control method?
- Used/taken any of the following within the last 30 days: Clotrimazole, Monistat, Azo, Monistat, Tioconazole, or anything similar?
- Menstrual Characteristics (Menstrual Cycle, Had 3 consecutive periods?)
- How often, Average length, Usual flow; number and Percentage women outside normal range
- Usual level of discomfort caused by cramping and other discomforts
- Spotting between periods
- Sexually Transmitted Diseases (Any history STDs? History of Gonorrhea? History of Chlamydia?)
- PAP smear (Had a normal PAP or ASC-US with negative high risk HPV test result within the appropriate screening timeframe?)
- Were the results of the PAP Normal?
- Number of live births (Natural) and number of live births (C-Section)
- Still breastfeeding?
- Had two consecutive menses since last delivery?
- Any daily discomfort that can be attributed to gynecological issues (non-menstrual)?
- If any, what is the level of this daily discomfort?

The number and percentage of subjects will be provided for each response to the question for categorical data, and 6-number statistics for continuous data.

3.5.4 Gynecological Examination

Gynecological examination will be performed during the screening visit and/or the date of VeraCept placement (before the procedure) in the following areas, and the results at the last assessment before the device placement will be summarized categorically.

- Vulva (Normal, Abnormal)
- Vaginal (Normal, Abnormal)
- Cervix (Normal, Abnormal)
- Adnexae (Normal, Abnormal)
- Uterus (Normal, Abnormal)
- Uterine irregularities found? (Yes, No)

3.5.5 Prior Medications

All medications taken by the subject pre-trial and during the study will be recorded on the prior and concomitant medication CRF page. Prior medications are medications that were

taken before the study device VeraCept placement, and concomitant medications are medications taken on or after the placement. A medication may be both “prior” and “concomitant” if the subject took it before the placement and continued taking it during the study. See section 3.6 for more details on concomitant medications.

All medications recorded on the CRF will be coded to the therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug Dictionary, March 2014 version. The number and percentage of subjects who had prior medications that were coded to each generic drug name and therapeutic drug class, as well as the number and percentage of subjects who had at least one prior medication will be presented. Subjects reporting more than one drug in each drug class/generic name are only counted once to that drug class/generic name.

A table with number and percentage of subjects with pain medication use prior to VeraCept IUD insertion will be provided. A list of medications used by subjects who failed the insertion procedure will also be presented.

3.6 Concomitant Medications

As defined in the Section 3.5.5, concomitant medications are medications taken on or after VeraCept placement. Similar to prior medications, concomitant medications will be summarized for Safety populations by the number and percentage of subjects in each coded drug name and drug class.

Another summary table will be presented for medications taken both before the study start and during the study.

3.7 Efficacy Analyses

3.7.1 Efficacy Analyses for Year 1 Data

Primary efficacy analysis was performed for the first year of the study (through Day 364) for Evaluable for Pregnancy population, by using Pearl Index. Pearl Index is defined as the number of pregnancies in 100 woman-years of method use. Pearl Index was calculated in subjects aged 18-35 at the time of VeraCept placement through the date of VeraCept removal or pregnancy, excluding the following cycles, unless the subject became pregnant in that cycle:

- When back-up contraception use was documented on the daily diary
- When the subject had no intercourse.

The Pearl Index formula is:

$$r = \frac{n}{L} \times 1300 = \frac{\text{Number of pregnancies}}{\text{Number of woman-cycles of pregnancy-risk}} \times 1300$$

where n is the number of pregnancies, and L is the number of woman-cycles, i.e., sum of the number of cycles each woman used the VeraCept up to and including the cycle of conception or until the time of VeraCept removal/expulsion, whichever comes earlier. The cycles of pregnancy-risk will be calculated as (Date of VeraCept removal/expulsion – Date of VeraCept placement + 1) / 28 for women who are not pregnant, and as (Date of pregnancy – Date of VeraCept placement + 1) / 28 for women who became pregnant

during the study. On-treatment pregnancies are defined to be pregnancies for which the estimated date of conception was within 7 days after study device expulsion or removal (the earlier of expulsion and removal dates will be used). The last cycle of pregnancy-risk can be a partial cycle and the partial cycle at risk is determined by dividing the number of days at risk in the cycle by 28 (e.g., 14/28 = 0.5 cycle of risk). If a cycle has a day with no information about backup contraception, that cycle will be excluded from the analysis (unless the subject became pregnant in that cycle).

To get the confidence interval (CI) for the Pearl Index, first the CI for the n (number of pregnancies) will be approximated by Poisson distribution sample mean's CI as

$$\left(\frac{\chi^2(\alpha/2; 2n)}{2}, \frac{\chi^2(1-\alpha/2; 2n+2)}{2} \right),$$

where $\chi^2(\alpha/2; 2n)$ in the lower limit is the Chi-square distribution (degrees of freedom = 2n) percentile with lower tail area (probability) α/2, and $\chi^2(1-\alpha/2; 2n+2)$ in the upper limit is similarly defined. If n = 0, the lower limit will be set as 0.

Then the 95% CI for Pearl Index will be estimated as follows by set α = 0.05.

$$\left(\frac{\chi^2(\alpha/2; 2n)}{2} \text{ / L x 1300}, \frac{\chi^2(1-\alpha/2; 2n+2)}{2} \text{ / L x 1300} \right)$$

The summary table will present the number of subjects in the EP analysis population, number of pregnancies and the number of cycles of risk in addition to the Pearl Index and its 95% CI, for the following 3 scenarios:

- All EP subjects
- EP subjects with at least one live birth
- EP subjects never had live birth

Life-Table (Kaplan-Meier) method will also be used to present probabilities of pregnancy through 1-year (13 cycles) interval (through Day 364). The Evaluable for Pregnancy population will be used for the analysis and cycles will be compressed to provide contiguous cycles.

All efficacy analyses will be first done for all EP population, and then done by parity for 2 sub-groups of EP population: one sub-group subjects who had live child birth, and the other sub-group subjects who had not.

3.7.2 Efficacy Analyses for the Whole Study

Post-Year 1 sexual activity and contraceptive use information can be found in the Cycle Contact CRF, which was added since the Extension study (Year 2) started, i.e., this CRF wasn't present from the beginning of the study, but added as a mid-study change. Each record in this form is for one cycle and has the following 2 key questions for determining if a cycle is pregnancy-risk or not:

- Did the subject have intercourse at least once during the cycle? (Yes, No)
- Did the subject use backup contraception during the cycle? (Yes, No)

If the answer is “Yes” to the first question and “No” to the second question, or the subject was pregnant within a cycle (determined form the Pregnancy Test form), that cycle will be considered as a pregnancy-risk cycle; otherwise, the cycle will not be considered as a pregnancy-risk cycle.

For cycles without any Cycle Contact information, e.g., neither of the above 2 “Yes”/“No” questions were answered and a subject wasn’t pregnant within the cycle either, the following procedure will be used to do the estimate for the subject:

A. find the total number of such type of cycles for that subject
B. find proportion of pregnancy-risk cycles from Year 1 diary data of the subject, which will be calculated as the number of pregnancy-risk cycles divided by the total number of cycles from Diary CRF
C. The number from Step A is multiplied by the number from Step B, and then rounded to 1 decimal place, which will be the estimated number of pregnancy-risk cycles where Cycle Contact information is missing for the subject.

The number from Step C will be added to the number of pregnancy-risk cycles from those without missing Cycle Contact information, and then added to the Year 1 pregnancy-risk cycles from Diary CRF data to get denominator value of the Pearl Index for Year 2 (data cut off at 26 cycles) and Year 3 (data cut off at 39 cycles). The numerator will be the number of on-treatment pregnancies by the end of Cycle 26 and Cycle 39, respectively.

The Year 2 and Year 3 analyses will also be performed without inclusion of cycles with missing Cycle Contact information, i.e., not doing estimates of pregnancy-risk through the above Steps A, B, and C.

The 95% Confidence Intervals for the Pearl Index will be calculated, by using the formula in the above Section 3.7.1, at the following 3 scenarios:

- All EP subjects
- EP subjects with at least one live birth
- EP subjects never had live birth

Life-Table (Kaplan-Meier) method will also be used to present probabilities of pregnancy-free through Year 1 (Day 365), Year 2 (Day 730), and Year 3 (Day 1095 + 2 weeks, or Study Day 1109). If a subject doesn’t have an on-treatment pregnancy, the event time will be censored at that day (of study device removal, or day of last contact).

3.8 Safety and Other Outcome Measures Analyses

All safety analyses will be done for the Safety population unless noted otherwise.

3.8.1 Treatment Exposure

Based on the Procedure CRF data as follows, number and percentage of subjects with VeraCept successfully placed will be presented for ITT and Safety populations.

- Was device deployed (at first try)? (Yes, No)
- If No, will a second attempt be made? (Yes - today, Yes - another visit, No)
- Was device deployed at second attempt? (Yes, No)

- VeraCept successfully placed

Furthermore, number of cycles (28 days = 1 cycle) with VeraCept use will be summarized by the 6-number statistics for Safety population.

3.8.2 Adverse Events and Serious Adverse Events

A treatment-emergent adverse event, or adverse event (AE) for simplicity, is any symptom, sign, illness, or experience that develops or worsens in severity and/or frequency after the study product VeraCept placement. A serious adverse event (SAE) is any AE that results in any of the following outcomes: Death; immediate threat to life; inpatient hospitalization or prolongation of an existing hospitalization; persistent or significant disability/incapacity; congenital anomaly/birth defect, ectopic pregnancy. All AEs will be coded with system organ class (SOC) and preferred term (PT) from the MedDRA Version 17.0.

Incidence of AEs and SAEs will be summarized by SOC and PT with the number and percentage of subjects with each SOC and PT. The following tables will be presented for Safety population:

- AEs by SOC and PT (will be done for the ITT and Safety populations)
- SAEs by SOC and PT
- AEs that led to study discontinuation or death by SOC and PT
- AEs by SOC and PT by severity
- Dyspareunia by onset time (within Year 1, Year 2, Year 3)
- Allergy-related symptoms (MedDRA high level group terms = Allergic conditions) by onset time (within Year 1, Year 2, Year 3) and by severity
- AEs by SOC and PT by relatedness to the study product AEs in descending order of SOC frequencies (no PT displayed)
- AEs in descending order of PT frequencies (no SOC displayed)
- Year 1 AEs (all AEs onset from study start through Study Day 365) in descending order of PT frequencies (no SOC displayed)
- Year 2 AEs (all AEs onset from Study Day 366 through Study Day 730) in descending order of PT frequencies (no SOC displayed)
- Year 3 AEs (all AEs onset from Study Day 371 through Study Day 1095) in descending order of PT frequencies (no SOC displayed)

All the above tables (except for where specified) are counting number of distinct subjects in each SOC and PT. Subjects reporting more than one AE/SAE in each PT will be counted only once to that PT, using the most severe intensity, for unique number of subjects counting. The only exception to this will be for the summary by relatedness to the study product, where subjects will be counted only once using the strongest relatedness to the study product for the purpose of counting distinct number of subjects. The same principle also will be applied to the summary at the SOC level.

An overall AE high-level summary table will also be provided for both ITT and Safety populations with total number and percentage of distinct subjects (but no SOC or PT) for:

- AE onset time frame (By Day 42/Week 6, From Day 43 through Day 91/Week 13, From Day 92 through Day 182/Week 26, Day 183 and later)
- AE severity (Mild, Moderate, Severe)
- AE relatedness (Not Related, Unlikely Related, Probably Related, Related)
- Related AEs (including Unlikely Related, Probably Related, Related) onset time by cycle (Cycle 1 through Cycle 13).
- SAE
- Discontinued study due to any AE
- Death due to any SAE.

Another high-level summary table for both ITT and Safety populations will present the counts of events (not distinct subjects) as following chart. Note that each percentage, if provided, is based on the number on the one where "(100.0)" is displayed. This AE summary table provides the cross reference between every level of relatedness and severity.

Relatedness	AE Severity			
	Mild	Moderate	Severe	Total # (%) of Events
Not Related	xx	xx	xx	xx (x.x)
Unlikely Related	xx	xx	xx	xx (x.x)
Probably Related	xx	xx	xx	xx (x.x)
Related	xx	xx	xx	xx (x.x)
Total # (%) of Events	xx (%)	xx (%)	xx (%)	xx (100.0)

Two listing-style tables, one is for SAEs, and the other is for AEs that led to premature study discontinuation, will also be presented, with the details about the event onset date, resolved date, days of onset since the VeraCept placement, severity, outcome, treatment for the AE, and relatedness to the study device, as well as other supportive data such as the subject's age and number of days on study.

3.8.3 Device Placement & Removal, Subject Pain

The easiness of VeraCept placement and removal, as well as subject pain during the procedure, is evaluated. Assessments (with possible results) during placement are:

- Were there any difficulties with device deployment? (Yes, No)
- How easy was the device placement (as rated by clinician doing the placement)? (Very Easy, Easy, Neither Easy nor Harder, Hard, Very Hard)
- Device placement pain (as rated by the subject)? (No Pain, Some Pain, Painful, Moderately Painful, Very Painful)
- Did the subject require mechanical dilatation? (Yes, No)

Assessments (with possible results) during the removal:

- VeraCept removal ease? (Very Easy, Easy, Neither Easy nor Hard, Hard, Very Hard)

- VeraCept removal pain (as rated by the subject)? (No Pain, Some Pain, Painful, Moderately Painful, Very Painful)
- Device expelled? (Yes, No)

The results will be summarized categorically with number and percentages of subjects in each categorical result for all these assessments. Cumulative VeraCept safety-related removal and expulsion rates at 1-year, 2-year, and 3-year will also be presented.

3.8.4 Device Expel and Subject Discomfort

All enrolled subjects will record device expel and discomfort through a daily diary:

- Experienced any unusual abnormal pain or pelvic pain or cramping? (None, Cramping Only, Pelvic Pain Only, Both Cramping and Pelvic Pain)
- Rate the discomfort (None, Mild, Moderate, Severe)
- Did the VeraCept device expel? (No, Yes, Suspected)

For each category of the question's answer (e.g., "Pain", Cramping", etc., all but "None" and "No"), the total number of days with that answer will be tabulated by cycle for each subject. If a cycle has less than 28 days but at least 14 days data, missing value will be imputed by the average in the same cycle for the subject, and then rounded to nearest integer.

For example, a subject at Cycle 6 has only 20 days data, of which 3 days with "Cramping". Then the total number of "Cramping" days at this cycle for her will be estimated as:

$$3 + (3 / 20 \times (28 - 20)),$$

which will be 4 after rounding to integer.

The six-number summary statistics will be presented by cycle for each parameter (i.e., categorical answer, all but "None" and "No"). Cumulative VeraCept device expulsion rates (%) at 1-year, 2-year, and 3-year will also be presented, which will be calculated as:

Subjects with device expulsion / # Subjects still in the study by that time-point x 100.

3.8.5 Bleeding and Spotting

Vaginal bleeding and spotting will be recorded daily by subjects in daily diary. The total number of bleeding or spotting days for each subject at each cycle, including the missing value imputation at cycles with less than 28 days but at least 14 days data, will be calculated similarly as the above Section 3.8.4, and then summarized by 6-number statistics for ECYC population. In addition, bleeding and spotting will be summarized separately. Subjects who discontinue the study due to bleeding complaints prior to completing one 28-day cycle will be included in the bleeding analysis.

3.8.6 Vital Signs and Weight

Vital signs measurements include pulse rate, body temperature, systolic and diastolic blood pressure. Along with weight and BMI, they are assessed at screening and at following visits and may be unscheduled visits, if needed:

- Visit 1 (Screening Visit)

- Visit 2 (Placement Visit)
- Visit 3 (Week 6)
- Visit 4 (Week 13)
- Visit 5 (Week 26)
- Visit 6 (Week 52) or Early Discontinuation
- Long Term Follow up 1 (Year 2, Month 6)
- Long Term Follow up 2 (Year 2, Month 12)
- Long Term Follow up 3 (Year 3, Month 6)
- Long Term Follow up 4 (Year 3, Month 12)

Based on the visit window in the study protocol, new analysis visit windows are redefined as follows to cover every data point, including unscheduled visits.

Analysis Visit Windows for Safety and Other Outcome Measure Analyses

Visit	Target Day (of Study Day*)	Analysis Visit Window	Visit (Window) in Protocol
Visit 1/Screening		-1 or earlier	Visit 1/Screening
Visit 2	1	1	Visit 2 (Day 1)
Visit 3	42	2 – 67	Visit 3 (Week 6±2)
Visit 4	91	68 – 137	Visit 4 (Week 13±2)
Visit 5	182	138 – 273	Visit 5 (Week 26±2)
Visit 6	364	274 – 385	Visit 6 (Week 52±2)
Long Term FU 1	548	386 – 638	LTFU 1/Year 1 Month 6
Long Term FU 2	730	639 – 823	LTFU 2/Year 1 Month 12
Long Term FU 3	913	825 – 1003	LTFU 3/Year 2 Month 6
Long Term FU 4	1095	1004 +	LTFU 4/Year 2 Month 12

* Study Day = Visit Date – VeraCept Placement Date + 1, for date on or after the study device placement; it = Visit Date – VeraCept Placement Date, for date before the study device placement.

Note that if there are 2 or more non-missing records in the same analysis visit window, only the last one (by the assessment date) will be used for summary table, but data listings will include all of them.

Body mass index (BMI) will be calculated numerically (= Weight in kilogram / square of Height in meter) and then categorized as: Underweight (< 18.5), Normal (18.5 – 24.9), Overweight (25.0 – 29.9), and Obese (≥30.0). Both numerical and categorical summaries for BMI will be presented. The 6-number summary statistics for continuous variables and their changes from baseline, as well as the number and percentage of subjects in each BMI category (Underweight, Normal, Overweight, and Obese), will be presented by analysis visit.

3.8.7 Physical Examination

Physical examination will be performed at the same visits as vital signs in the following body areas:

- General Appearance
- Skin
- HEENT
- Thyroid
- Lung
- Back
- Heart
- Abdomen
- Extremities
- Neurological

The examination results (“Normal” or “Abnormal”), and changes from baseline (“Improved” – if “Abnormal” at baseline and “Normal” at post-baseline, “No Change”, “Worsened” – if “Normal” at baseline and “Abnormal” at post-baseline), will be summarized by presenting the number and percentage of subjects in each category by body area at each analysis visit.

3.8.8 Pelvic Examination

Pelvic examination will be performed at the same visits as vital signs to verify the VeraCept position with the following 3 questions on the CRF (in addition to those in the “Gynecological Examination” section 3.5.4, which were assessed at baseline visit only).

- Was a Transvaginal Ultrasound Performed? (Yes, No)
- Was a Manual String Check performed? (Yes, No)
- Is the device in the proper position? (Yes, No)

The device in the proper position will be summarized categorically by analysis visit. The pelvic exam methods will also be summarized by presenting the number and percentage of subjects who had

- only ultrasound performed
- only manual string check performed
- both ultrasound and manual string check performed.

3.8.9 Monthly Phone Contact

Monthly phone contact will be carried out for 1 year (12 months) since the study device placement. The data summary (where months are defined as 30-day intervals from VeraCept placement date) will include the following 3 questions by presenting the number and percentage of subjects in each category for the first 2 questions, and 6-number statistics for the last one.

- Was there a need for additional contraception? (Yes, No)
- Did you have intercourse at least one time in the last month? (Yes, No)
- Approximately how many times since the last phone call have you had intercourse?

3.8.10 Long Term Follow Up Visits

Long term follow-up office visits for additional 2 years will occur every 6 months for those subjects who continue study device use after 1 year (52 weeks). In addition to vital signs, physical exam, pelvic exam, etc., as those shown in Section 5.1 “Study Schedule of Assessments”, the assessments also include the following 3 questions which will be summarized categorically with number and percentage of subjects provided for each answer.

- Did you have vaginal intercourse at least once since your last visit? (Yes, No)
- Did you use any additional birth control methods in the past 6 months? (Yes, No)
- How often has the subject had vaginal intercourse in the past 6 months? (Not Once, Once a month or less, Several Times a Month, Once or Twice a week, Several Times a week, At least once a day)

3.8.11 Cycle Contact

In addition to being used in the efficacy analysis for EP population, cycle contact data will be summarized by the number and percentage of “Yes” and “No” answers to each question by contact cycle for Extension population subjects.

3.8.12 Return to Fertility

Any subject who discontinues for desire to get pregnant will have a follow-up call to be completed 6 months after discontinuing. In addition to data listing, the following summaries will also be presented, with the percentages (%) based on the total number of subjects who discontinue due to desire to get pregnant:

- Number (%) of subjects got pregnant
- Number (%) of subjects got pregnant in 1, 2, 3, 4, 5 and 6 months
- Number (%) of subjects did not get pregnant
- Number (%) of subjects with 1, 2, 3, 4, 5 and 6 months of follow-up for those not pregnant.

3.8.13 Pregnancy Tests and Outcomes

All urine pregnancy test results, serum pregnancy test results, notification and outcome data, will be presented in data listings.

4.0 REFERENCES

1. Higgins JE., Wilkens LR., Statistical comparison of Pearl rates. Am J Obstet Gynecol. 1985; 151:656-9.
2. Hubacher D, Reyes V, Lillo S, et al. Preventing copper intrauterine device removals due to side effects among first-time users: randomized trial to study the effect of prophylactic ibuprofen. Hum Reprod. 2006;21: 1467–1472
3. Jones J, Mosher WD and Daniels K, Current contraceptive use in the United States, 2006–2010, and changes in patterns of use since 1995, National Health Statistics Reports, 2012, No. 60, <http://www.cdc.gov/nchs/data/nhsr/nhsr060.pdf>

4. Secura G, Alllsworth J, Madden T, et al. The Contraceptive CHOICE Project: reducing barriers to long-acting reversible contraception. Am J Obstet Gynecol. 2010 Aug; 203(2): 115.e1–115.e7.

5.0 APPENDICES

5.1 Study Schedule of Assessments

	Visit 1 - Screen	Visit 2- (VeraCept Placement) Day 1	Visit 3 - Follow up Week 6 ± 2	Visit 4 – Follow up Week 13 ± 2	Visit 5 – Follow up Week 26 ± 2	Visit 6 – Follow up Week 52 ± 2 / Exit	Phone Visit (Optional) up to 52 Weeks	Monthly Phone Contact up to 52 Weeks	Long-term FU post 52-week visit (Every 6 Months 18-30 (±4wks) and 3 yrs (-3wks/+4wks) /Exit visit	End of each 28-day Cycle Contact (Post 52 Wks ± 1w)
Initiation/Subject Characteristics										
Assessment of Eligibility	X	X					X			
Distribution of information	X									
Informed consent, PHI and Bill of Rights forms	X									
Demographics and baseline characteristics	X									
Medical/surgical, gynecologic and menstrual history	X									
Safety and Effectiveness										
Vital signs and weight	X	X	X	X	X	X			X	
Height	X									
General physical exam	X	X	X	X	X	X			X	
Pelvic exam	X	X	X[1]	X[1]	X[1]	X[1]			X[1]	
Cervical cytology	X									
Cervical infection tests	X[6]									
Transvaginal ultrasound (for verifying study device position)		X	X[2]	X[2]	X[2]	X			X[2]	
Pregnancy test-urine	X	X	X	X	X	X | X[4]		X	X	
Prior and interval concurrent medication	X	X	X	X	X	X		X	X	
Adverse events		X	X	X	X	X		X	X	

	Visit 1 - Screen	Visit 2- (VeraCept Placement) Day 1	Visit 3 - Follow up Week 6 ± 2	Visit 4 – Follow up Week 13 ± 2	Visit 5 – Follow up Week 26 ± 2	Visit 6 – Follow up Week 52 ± 2 / Exit	Phone Visit up to 52 Weeks (Optional)	Monthly Phone Contact up to 52 Weeks	Long-term FU post 52-week visit (Every 6 Months 18-30 (±4wks) and 3 yrs (-3wks/+4wks) /Exit visit	End of each 28-day Cycle Contact (Post 52 Weeks ± 1 w)
Other										
IUD placement ease		X								
IUD placement pain		X								
IUD removal ease						X				
IUD removal pain						X				
Concomitant contraception		X	X	X	X	X	X	X	X	X
Need for contraception (intercourse)	X	X	X	X	X	X	X	X	X	X
Diary dispensing	X[3]	X	X	X	X					
Diary collected/reviewed with patient (subject)		X[3]	X	X	X	X		X		
End of study medication						X				

Note: Screening and enrollment visit *may be combined* if the patient requests and all labs and screening exams are documented as normal.
Note: If VeraCept is removed before 52+2 weeks, Visit 6 activities should be completed for Exit Visit.

1 Pelvic exam for VeraCept string check
2 Transvaginal Ultrasound only if indicated
3 First Diary Dispensing and Collection, prior to VeraCept placement, to be used as training with the subject. This diary data is not a part of data collection or analysis. It is intended to ensure the subject understands how to complete the diary during the follow up period.
4 Urine pregnancy test will be done 17 days after removal/study exit by the subject at home, with a follow up call by the study coordinator or PI required to document the results.
5 Screening for cervical infection tests are to be done at screening unless these tests have been previously completed within three months of the screening visit. Results must be negative.

5.2 Table of Contents for Data Display

Following is the list of planned tables, listings, and figures. Tables will be numbered according to the nomenclature used to support the final clinical study report.

The format of each unique table is provided in a separate document of “Table Shells”, but no data listing shells or figure shells are provided. Some outputs from statistical programming may be slightly different in layout from that of illustrated in “Table Shells”. The table shells will not be amended to match the actual tables in such cases.

Table Number	Table Title	Analysis Population
14.1.1	Summary of Subject Disposition and Reasons for Discontinuation	All Screened
14.1.2	List of Subjects Who Prematurely Discontinued the 1-Year Study	ITT
14.1.2Ext	List of Subjects Who Prematurely Discontinued the 3-Year Study	Extension
14.1.3	Summary of Subject Disposition at 1-Year by Study Site	ITT
14.1.3Ext	Summary of Subject Disposition at 3-Year by Study Site	Extension
14.1.4	Number and Percentage of Subjects at Each Scheduled Study Visit	ITT
14.1.5	Number and Percentage of Subjects with Protocol Deviations	ITT
14.1.6	Summary of Analysis Populations	ITT
14.1.7	Demographics and Pre-Treatment Characteristics	ITT
14.1.7EP	Demographics and Pre-Treatment Characteristics	EP
14.1.7ECYC	Demographics and Pre-Treatment Characteristics	ECYC
14.1.8.1	Medical History	ITT
14.1.8.2	Gynecological History	ITT
14.1.9	Gynecological Examination	ITT
14.1.10.1C	Number and Percentage of Subjects with Prior Medication Use by Drug Class in Descending Order of Frequencies	ITT
14.1.10.1	Number and Percentage of Subjects with Prior Medication Use by Drug Class and Generic Name	ITT
14.1.10.1P	Number and Percentage of Subjects with Pain Medication Use Prior to VeraCept IUD Insertion	Safety

14.1.10.2C	Number and Percentage of Subjects with Concomitant Medication Use by Drug Class in Descending Order of Frequencies	Safety
14.1.10.2G	Number and Percentage of Subjects with Concomitant Medication Use by Generic Name in Descending Order of Frequencies	Safety
14.1.10.2	Number and Percentage of Subjects with Concomitant Medication Use by Drug Class and Generic Name	Safety
14.1.10.3C	Number and Percentage of Subjects with Prior Medications Also Used After Study Device Placement by Drug Class in Descending Order of Frequencies	ITT
14.1.10.3	Number and Percentage of Subjects with Prior Medications Also Used After Study Device Placement by Drug Class and Generic Name	Safety
14.1.10.4	List of Medications Used by Subjects who Failed the Insertion Procedure	ITT
14.2.1-Y1	1-Year Pearl Index	EP
14.2.1-Y2	2-Year Pearl Index - No Missing Cycle Contact	EP
14.2.1-Y2M	2-Year Pearl Index – with Estimation for Missing Cycle Contact	EP
14.2.1-Y3	3-Year Pearl Index – No Missing Cycle Contact	EP
14.2.1-Y3M	3-Year Pearl Index – with Estimation for Missing Cycle Contact	EP
14.3.0	Treatment Exposure	Safety
14.3.0T	Treatment Exposure	ITT
14.3.1.1	Overall Number and Percentage of Subjects with Adverse Events	Safety
14.3.1.1T	Overall Number and Percentage of Subjects with Adverse Events	ITT
14.3.1.2	Overall Number of Adverse Events by Severity and Relatedness to the Study Product	Safety
14.3.1.2T	Overall Number of Adverse Events by Severity and Relatedness to the Study Product	ITT
14.3.1.3C	Summary of Adverse Events by System Organ Class in Descending Order of Frequencies	Safety
14.3.1.3P	Summary of Adverse Events by Preferred Term in Descending Order of Frequencies	Safety

14.3.1.3P-Y1	Summary of Year 1 Adverse Events by Preferred Term in Descending Order of Frequencies	Safety
14.3.1.3P-Y2	Summary of Year 2 Adverse Events by Preferred Term in Descending Order of Frequencies	Safety
14.3.1.3P-Y3	Summary of Year 3 Adverse Events by Preferred Term in Descending Order of Frequencies	Safety
14.3.1.4	Summary of Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.4T	Summary of Adverse Events by System Organ Class and Preferred Term	ITT
14.3.1.5	Summary of Serious Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.6	Summary of Adverse Events that Led to Premature Study Discontinuation	Safety
14.3.1.7C	Summary of Adverse Events by System Organ Class and by Severity	Safety
14.3.1.7	Summary of Adverse Events by System Organ Class and Preferred Term and by Severity	Safety
14.3.1.8C	Summary of Adverse Events by System Organ Class and by Relatedness to the Study Product	Safety
14.3.1.8	Summary of Adverse Events by System Organ Class and Preferred Term and by Relatedness to the Study Product	Safety
14.3.1.9A	Summary of Allergy-Related Symptoms by Onset Time	Safety
14.3.1.9B	Summary of Dyspareunia by Onset Time	Safety
14.3.2.1	List of Serious Adverse Events	Safety
14.3.2.2	List of Adverse Events that Led to Premature Study Discontinuation	Safety
14.3.5	Device Placement and Subject Pain During the Procedure	Safety
14.3.6	Device Expulsion or Removal and Subject Pain During the Procedure	Safety
14.3.7	Number of Days for Subject with Discomfort by Cycle	Safety
14.3.8	Number of Days for Subjects with Bleeding and Spotting by Cycle	ECYC
14.3.9	Vital Signs and Weight by Analysis Visit	Safety
14.3.10	Physical Examination by Analysis Visit	Safety
14.3.11	Summary of Pelvic Examination	Safety

14.3.12	Summary of Monthly Phone Contact	Safety
14.3.13	Summary of Long Term Follow Up Visits	Extension
14.3.14	Summary of Cycle Contact	Extension
14.3.15	Summary of Return to Fertility	Safety

Listing Number	Listing Title	Analysis Population
16.2.1.1	Subject Disposition	All Screened
16.2.1.2	Eligibility	All Screened
16.2.1.3	Subject Study Visits	ITT
16.2.2	Protocol Deviations	ITT
16.2.3	Subjects Excluded from the Efficacy Analysis	ITT
16.2.4.1	Demographics	ITT
16.2.4.2	Medical History	ITT
16.2.4.3	Gynecological History	ITT
16.2.4.4	Prior and Concomitant Medications	ITT
16.2.5.1	VeraCept Placement	ITT
16.2.5.2	VeraCept Removal	Safety
16.2.6.1	Pregnancy Test	Safety
16.2.6.2	Pregnancy Notification	Safety
16.2.6.3	Pregnancy Outcome	Safety
16.2.7.1	Adverse Events	ITT
16.2.7.2	Serious Adverse Events	ITT
16.2.8.1	Subject Diary	ITT
16.2.8.2	Monthly Phone Contact	Safety
16.2.8.3	Follow-Up Visit CRF	Safety
16.2.8.4	Cycle Contact	Extension
16.2.8.5	Long Term Follow-up	Extension
16.2.9.1	Vital Signs	Safety
16.2.9.2	Physical Examination	Safety
16.2.9.3	Pelvic Examination	Safety
16.2.9.4	Return to Fertility	Safety

Figure Number	Figure Title	Analysis Population
14.2.2-Y1	Kaplan-Meier Curve for Pregnancy-free up to 12 Months	EP

14.2.2-Y2	Kaplan-Meier Curve for Pregnancy-free up to 24 Months	EP
14.2.2-Y3	Kaplan-Meier Curve for Pregnancy-free up to 36 Months	EP