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Statistical Analysis Plans

A Randomized, Single-Blind, Comparative Bioavailability Study to Assess the Pharmacokinetic Properties of VeraCept® Intrauterine Contraceptive vs ParaGard® in Healthy, Post-Menarcheal Women

DOCUMENT DATES: 21 November 2021 and 20 September 2024

Amended Pharmacokinetic Analysis Plan

A Randomized, Single-Blind, Comparative Bioavailability Study to Assess the Pharmacokinetic Properties of VeraCept® Intrauterine Contraceptive vs. ParaGard® in Healthy, Post-Menarcheal Women

Name of Investigational Drug:	VeraCept Intrauterine Contraceptive
Study Number:	CMDOC-0045
Sponsor:	Sebela Pharmaceuticals, Inc. 645 Hembree Parkway, Suite I Roswell, GA 30076
Pharmacokinetic Analysis Site:	Nuventra, LLC 2525 Meridian Parkway, Suite 200 Durham, NC 27713
Phase:	3
Version:	Amendment 2 Final
Date of Report:	05 November 2021

Analysis Plan Prepared By

SUMMARY OF CHANGES

Amendment/Date	Location	Description of Changes
Amendment 2 5 November 2021	Header	Updated "PK Analysis Plan" to "Amended Pharmacokinetic Analysis Plan"
	Title Page	Updated "Pharmacokinetic Analysis Plan" to "Amended Pharmacokinetic Analysis Plan" added Pharmacokinetic Analysis Site; updated version to Amendment 2; updated date from 02 October 2019 to 5 November 2021
	Summary of Changes	Updated to reflect changes made in PK Analysis Plan Amendment 2
	Approval Page	Updated Nuventra signatory from "Author" to "Project Lead"; updated "Nuventra, Inc." to "Nuventra, LLC"; removed address from all signature lines
	Table of Contents	Updated to reflect new sections and page numbers; added List of Tables and List of Figures
	Abbreviations	Updated to include additional abbreviations
	Section 1	Updated to include information about the 3-part analysis plan and the planned summary and reporting of safety data
	Section 3	Added Study Endpoints
	Section 5	Added information about PK blood collection during the Extension Phase
	Section 6	Included Changes to Protocol-Specified Population
	Section 8	Updated heading to emphasize NCA and statistical analyses focus on Treatment Comparison Phase, clarified use of actual dosing and sampling times for the final NCA; removed information about the Extension Phase from Statistical Analyses; added Changes to Protocol-Defined Analysis, Imputation of Missing Data, and Data Exclusions
	Section 9	Added Part C – Pharmacokinetic and Statistical Analyses During Extension Phase
	Section 10	Added Safety Data Summary and Reporting During Treatment Comparison Phase and Treatment Extension Phase
	Section 11	Updated to address the planned Tables, Figures, Listings, and Appendices for the PK data collected during the Extension Phase; added information

		about list of planned safety data summary tables and listings for the safety data
	Global	Added clarifying language to delineate analysis and reporting of pharmacokinetic and safety data; minor updates to reflect updates in Nuventra's PK analysis plan template and formatting
Amendment 1 02 October 2019	Title Page	Updated to match Nuventra's updated PK analysis plan template and formatting Updated to match the protocol title in protocol version 2.0
	Document Approval Page	Updated Nuventra signatory name and address
	Table of Contents	Added to this version
	Abbreviations	Added to this version
	Section 1	Updated to include planned interim analysis
	Section 3	Updated to match protocol version 2.0
	Section 4	Updated to match protocol version 2.0
	Section 6	Updated to include planned interim analysis
	Section 10	Updated to specify deliverables associated with interim and final analyses
	Header	Updated to include change in sponsor name
	Footer	Updated to match Nuventra's updated PK analysis plan template and formatting
	Throughout	Edits to correct headings, heading numbering, typographical errors, formatting, and clarify language

APPROVAL PAGE

Study Number: **CMDOC-0045**

Study Title: **A Randomized, Single-Blind, Comparative Bioavailability Study to Assess the Pharmacokinetic Properties of VeraCept® Intrauterine Contraceptive vs. ParaGard® in Healthy, Post Menarcheal Women**

Project Lead Signature:

[redacted]

05 Nov. 2021

Date

Sponsor Review and Approval:

[redacted]

_____

Date

_____

Date

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Events of Specific Interest
ANCOVA	Analysis of Covariance
BLQ	Below the Limit of Quantification
CI	Confidence Interval
CV%	Coefficient of Variation (given as a percentage)
IUD	Intrauterine Contraceptive Device
NCA	Noncompartmental Analysis
PK	Pharmacokinetic
SAE	Serious Adverse Event
SD	Standard Deviation
SOP	Standard Operating Procedures

PK parameter abbreviations can be found in Table 8-2 and Table 9-2

1. INTRODUCTION

This pharmacokinetic analysis plan describes the analysis and reporting of the pharmacokinetic (PK) results for study CMDOC-0045, in which the bioavailability of systemic copper exposure after insertion of Sebela's investigational VeraCept intrauterine contraceptive device (IUD) is compared to the marketed ParaGard IUD in healthy, post-menarcheal women.

Sebela has developed VeraCept to provide a long-acting, reversible method of contraception for non-pregnant, parous, and nulliparous women of child-bearing age. VeraCept's design utilizes a shape memory nitinol spring frame with the same active chemical entity as the marketed reference product, ParaGard (99.99% pure copper), yet containing less than half of the exposed copper surface area (175 mm^2). VeraCept is delivered preloaded in an introducer, which is narrower than the ParaGard inserter, to simplify clinician insertions and facilitate correct, easy placement in the uterus. Correct placement and a shape memory frame optimize VeraCept's long-term efficacy by decreasing expulsions and increasing its tolerability, thereby improving end-user continuation rates. In contrast to the passive plastic "T" utilized in ParaGard, VeraCept has been designed to mitigate the side effects associated with ParaGard without compromising contraceptive effectiveness.

The current study will assess systemic copper exposure after insertion of VeraCept as compared to ParaGard in enrolled subjects. The study will characterize the PK and comparative bioavailability of observed and baseline-corrected total serum copper exposure in patients after receiving either VeraCept or ParaGard.

This is a 3-part analysis plan with Part A addressing the planned interim PK analysis, Part B addressing the noncompartmental analysis (NCA) and statistical analysis of the PK data for the Treatment Comparison Phase and resulting final PK report, and Part C addressing the analyses on PK data collected during the Extension Phase.

In addition to PK analysis and reporting, the study will also monitor the safety of VeraCept and ParaGard in enrolled subjects. The safety sections of this PK analysis plan address the planned summary and reporting of the safety data for this study but detailed information, including the list of planned safety data summary tables and listings, can be found in the safety analysis plan authored by Synteract. The safety data summary tables and listings and the resulting safety conclusions will be generated by Synteract and will be included in the final PK report.

2. PHARMACOKINETIC OBJECTIVES

This analysis plan is based on the information provided in Protocol Version 2.0 (03 Jul 2019).

2.1 Primary Objective

The primary objective of the study related to the PK analysis is:

- To assess the relative bioavailability of observed systemic copper from VeraCept versus ParaGard based on Cmax, Cmean, and AUC0-56 days.

2.2 Secondary Objectives

The secondary objectives of the study related to the PK analysis are:

- To assess the relative bioavailability of baseline-corrected total serum copper from VeraCept versus ParaGard based on Cmax, Cmean, and AUC0-56 days.
- To assess the total serum copper levels within each treatment relative to the normal range (49 to 184 µg/dL).
- To assess the long-term stability of copper levels following insertion of VeraCept.

3. STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint related to the PK analysis is:

- Mean total serum copper concentration (Cmean), Cmax, and AUC0-56 days for observed copper for each treatment.

3.2 Secondary Endpoints

The secondary endpoints related to the PK analysis are:

- Mean total serum copper concentration (Cmean), Cmax, and AUC0-56 days for baseline-corrected copper for each treatment.
- Total serum copper concentrations within each treatment for each assessment day for 56 days.
- Mean total serum copper concentration for observed and baseline-adjusted copper for each treatment over 5 years (Treatment A, VeraCept IUD only).

4. INVESTIGATIONAL PLAN

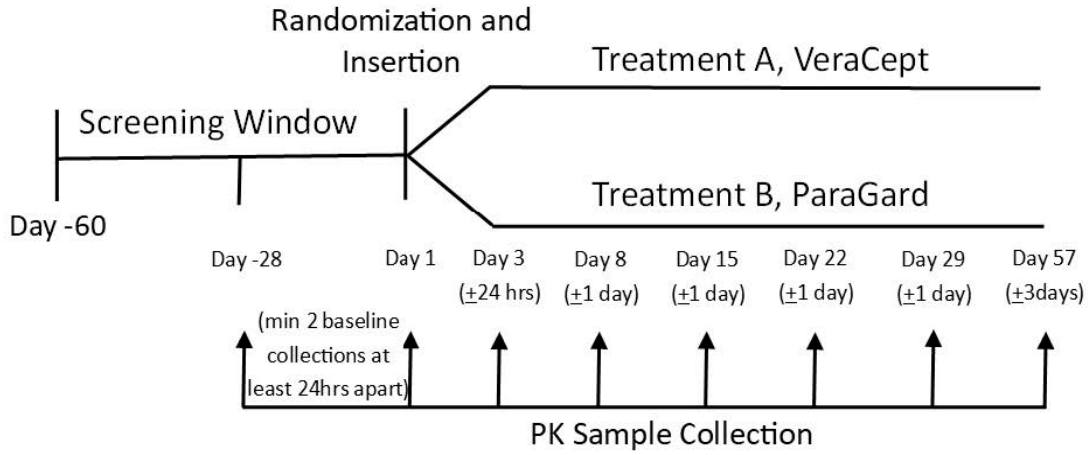
4.1 Overall Study Design

This parallel, open-label study is designed to evaluate the comparative bioavailability of systemic copper exposure after insertion of VeraCept versus ParaGard in post-menarcheal women. Up to 40 subjects will receive one of two treatments (A or B) as described below:

- Treatment A (N=20): VeraCept® IUD, test (referred to as VeraCept)
- Treatment B (N=20): ParaGard® IUD, reference (referred to as ParaGard)

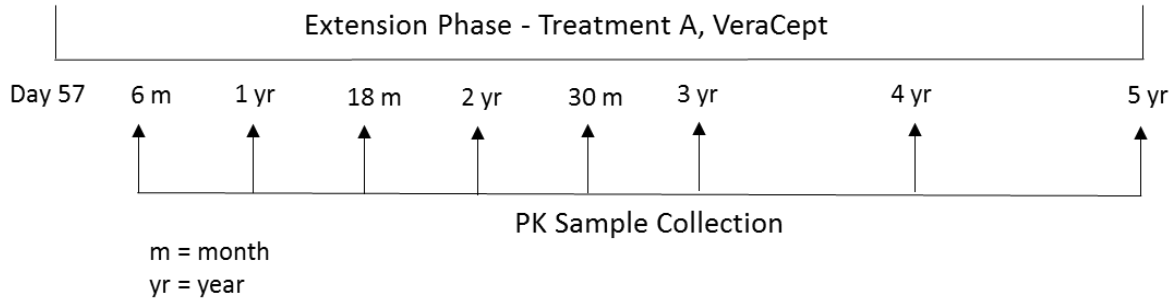
Figure 1 and Figure 2 display the study design schematic for the Treatment Comparison Phase and Extension Phase, respectively.

Figure 1 Study Design Schemata — Treatment Comparison Phase



Subjects will be screened within 60 days prior to the first insertion of study drug, and blood samples will be collected within 28 days from first insertion of study drug at two visits within this screening period to establish baseline copper concentrations. At least 24 hours should separate each baseline sample. On Day 1 of each treatment period, PK, safety, and baseline assessments will be collected prior to IUD insertion. Subjects will return to the clinic at 48 hours post-IUD insertion (Day 3(±24 hours)), and on Days 8 (±1 day), 15 (±1 day), 22 (±1 day), 29 (±1 day), and 57 (±3 days) for blood collection for measurement of total serum copper concentrations.

Figure 2 Study Design Schemata — Extension Phase



On Day 57, ParaGard subjects will exit the study and may continue ParaGard use per standard of clinical care. VeraCept subjects will continue in the extension phase of the study, intended to assess long-term stability of serum copper concentrations up to 5 years and monitor safety. During the first 3 years, subjects will return to the clinic every 6 months (±30 days) for clinical assessments and blood collection for measurement of total serum concentrations. Following Year 3, subjects will return annually, up to Year 5. During the extension phase, PK collections may occur anytime within 30 days of the planned collection time. Subjects prematurely discontinuing the study should follow the Early Discontinuation procedures specified in the protocol. Additional follow-up visits may be scheduled, as needed, if a subject has an ongoing significant adverse event (AE) and/or a clinically significant laboratory abnormality. A schedule of the study procedures and assessments to be conducted for each subject is provided in the Time and Events Table in the protocol.

Subjects will be randomized to a treatment group (VeraCept or ParaGard). The study will be conducted at one or more study sites. Participants will be randomly allocated in a 1:1 ratio, either to VeraCept or ParaGard. The randomization will be stratified by site, if needed, but centrally managed until 40 subjects have been randomized.

5. PHARMACOKINETIC SAMPLE COLLECTION

5.1 Blood Collection and Sample Processing

Two blood samples for PK analysis will be collected within 28 days from Day 1, and at least 24 hours apart within this screening period (can be performed on Screening and Day 1 visits prior to IUD insertion) to establish baseline copper concentrations, on Day 1 prior to IUD insertion, on Day 3, approximately 48 hours after insertion, and on Days 8, 15, 22, 29, and 57 at approximately the same time of day as the prior PK collections. Following the PK collections on Day 57, the PK samples for Months 6, 12, 18, 24, 30, 36, and 48 will be collected within 30 days of the planned collection day. Approximately 3-5 mL of whole blood will be collected for each blood draw. The total volume collected from each subject for all PK samples will be approximately 20 mL.

Blood samples will be collected in containers appropriate for serum collection, such as a “red topped” tube, which does not contain an anticoagulant.

5.2 Bioanalytical Methods for Pharmacokinetic Samples

Blood samples will be processed for serum as described in the PK laboratory manual. The yield of serum will be subdivided into 2 samples (~1 mL each). One of these samples will be shipped as soon as possible to the analytical lab for analysis of total serum copper, and the other will be stored at -20ºC at the site until completion of the study (or until directed by Sebela or designee), and then sent to the analytical lab in one group.

6. PHARMACOKINETIC POPULATION

6.1 Pharmacokinetic Population

The PK study population is defined as all randomized subjects for which all pre-insertion total serum copper concentrations were within the normal range (49 to 184 µg/dL), had an IUD placed successfully, and completed all scheduled PK sample collections without a protocol deviation or AEs that significantly impact the planned PK analyses.

6.2 Changes to Protocol-Specified Population

The protocol defines the overall PK study population but not the PK concentration and PK parameter populations.

The PK concentration population is defined as all randomized subjects that have an IUD placed successfully and have at least one quantifiable total serum copper concentration post-insertion. Concentration data from this population will be presented in the tables and used in the calculation of summary statistics for plotting purposes.

The PK parameter population is defined as subjects in the PK concentration population with sufficient data to calculate PK parameters (at least 4 quantifiable total serum copper concentrations and no protocol deviations that have a material impact on the PK). This population will be included in the NCA and individual copper concentration versus time figures.

Any other changes to protocol-specified population due to protocol deviations or other factors that may impact PK will be detailed in the final PK report.

7. PART A – INTERIM PHARMACOKINETIC AND STATISTICAL ANALYSES DURING TREATMENT COMPARISON PHASE

7.1 Noncompartmental Pharmacokinetic Analysis and Descriptive Statistics

An interim analysis for the Treatment Comparison Phase will be performed once approximately 20 subjects have completed the visit on Day 57. All interim PK analysis and reporting will be performed according to applicable Nuventra standard operating procedures and protocol specifications. PK parameters will be calculated by Nuventra using Phoenix® WinNonlin® 8.1 or later (Certara, Princeton, NJ, USA) using nominal doses and sampling times.

For these analyses, all relevant PK parameters from Section 8.1 and Tables, Listings, and Figures from Section 11 will be generated using Phoenix® WinNonlin®.

The mean of the two screening baseline values and the Day 1 pre-dose concentration will be used for baseline correction. Descriptive statistics (number of subjects [N], mean, standard deviation [SD], percent coefficient of variation [CV%], median, minimum, and maximum) will be used to summarize observed and baseline-corrected serum concentrations. All relevant parameters will be summarized using descriptive statistics (N, mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%). Parameters that are equal to zero will be reported as "missing".

No statistical analyses are planned for interim analyses.

8. PART B – FINAL PHARMACOKINETIC AND STATISTICAL ANALYSES DURING TREATMENT COMPARISON PHASE

8.1 Noncompartmental Pharmacokinetic Analysis and Descriptive Statistics

All final PK analysis and reporting for the Treatment Comparison and Extension Phases will be performed according to applicable Nuventra standard operating procedures and protocol specifications. PK parameters will be calculated using NCA implemented within a validated installation of Phoenix® WinNonlin® using actual dosing and sampling times. Programming of tables, figures, and listings will be performed using verified templated R code run in validated R Software and RStudio environments. Additional information on the software to be utilized in this study can be found in Table 8-1. The actual version of the software will be included in the final PK report. Additional software may be used, if necessary. All software used will be documented in the final PK report.

Table 8-1. Software List

Software	Use	Version	Company
Phoenix WinNonlin	NCA	V 8.1 or later (Validated as per VAL.001.04)	Certara (Princeton, NJ)
R Software	Input file generation	V 3.4.0 or later (custom code)	R Foundation for Statistical Computing (Vienna, Austria)
	TLFs	V 3.4.0 or later (Validated as per VAL.002.07)	
RStudio	TLFs	V 1.0.143 or later (Validated as per VAL.002.07)	RStudio (Boston, MA)
SAS	Biostatistics	SAS 9.4 or later	SAS Institute, Inc. (Cary, NC)

PK blood samples will be analyzed for total serum copper concentrations using validated bioanalytical methods. The mean of the two screening baseline values and the Day 1 pre-dose concentration will be used for baseline correction.

Descriptive statistics to summarize observed and baseline-corrected serum concentrations include: N (number of non-missing data), Mean (arithmetic mean), standard deviation (SD), arithmetic percent coefficient of variation (CV%), minimum, median, and maximum.

Summaries of plasma concentration data will include data for all subjects in the PK concentration population (see Section 6.2).

PK parameters for uncorrected and baseline-corrected serum copper will be calculated as described in Table 8-2.

Table 8-2. Pharmacokinetic Parameters

Parameter	Description
Data from Treatment Comparison Phase	
Cmax	Maximum observed concentration, observed by inspection of individual study participant serum concentration-time plots
Tmax	Time of maximum observed concentration, obtained directly from the observed concentration-time data
Cmean	Mean total serum copper concentration of samples collected after Day 1 (Days 3-57)
AUC0-56 days	Area under the concentration time curve, from time 0 (study Day 1) to the last measurable non-zero concentration up to 56 days (study Day 57), calculated by the linear trapezoidal method

Note that the abbreviations and definitions listed above may differ slightly from the protocol in the phrasing; however, the equations and methods used to generate these parameters do not differ from the protocol.

Additional PK parameters may be calculated, as necessary, to fully characterize the PK profiles of uncorrected and baseline-corrected serum copper and will be defined in the final PK report.

No PK parameters will be calculated for subjects with fewer than 4 quantifiable total serum copper (uncorrected) concentrations following imputation of concentrations below the limit of quantification (BLQ) (see Section 8.4). Baseline-corrected copper PK parameters will be calculated for all subjects regardless of the number of non-zero concentrations.

All subjects in the PK parameter population (see Section 6.2) will be included in the descriptive statistics for the PK parameters. PK parameters will be listed for each subject by treatment, and the following descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, SD, CV%, median, minimum, and maximum. Geometric mean and geometric CV% will be calculated for continuous PK parameters. Tmax will be presented as N, median, minimum, and maximum. Parameters that are equal to zero will be reported as "missing".

8.2 Statistical Analyses

For the primary analysis, an analysis of covariance (ANCOVA) model with fixed effects for treatment and Day 1 pre-insertion concentration as a continuous effect will be used to analyze the uncorrected PK parameters Cmax, Cmean, and AUC0-56 days. As such, a point estimate of the difference between treatments and a 90% confidence interval (CI) of the difference will be provided.

For the secondary analysis, an ANCOVA model with fixed effects for treatment and natural log (ln) transformed Day 1 pre-insertion concentration as a continuous effect will be used to analyze the ln transformed corrected PK parameters Cmax, Cmean, and AUC0-56 days. For each treatment comparison, a point estimate and 90% CIs will be provided for the geometric least squares mean ratio upon back-transformation.

In addition, for each PK assessment day, the number and percentage of PK assessments within the total serum copper normal range (49 to 184 µg/dL) will be assessed for each treatment. A shift table will also be provided for each of the PK days post Day 1 relative to the normal range.

8.3 Changes to Protocol-Defined Analysis

No changes to the protocol-defined analysis are planned at this time. Any changes will be detailed in the final PK report.

8.4 Imputation of BLQ Values

For the calculation of mean concentrations and generation of mean concentration versus time profiles, all BLQ values will be set to zero, except when an individual BLQ falls between two quantifiable values, in which case it will be treated as missing data.

For the PK analysis and individual concentration versus time plots, a concentration that is BLQ is assigned a value of zero if it occurs in a profile before the first measurable concentration. If a BLQ value occurs after a measurable concentration in a profile and is followed by a value above the lower limit of quantification, then the BLQ is treated as missing data. If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration), it is treated as missing data. If 2 BLQ values occur in succession after Cmax, the profile is deemed to have terminated at the first BLQ value, and any subsequent concentrations are omitted from PK calculations.

In circumstances where alternative approaches to handling BLQ data are necessary, the relevant modifications will be appropriately documented in the clinical study report or final PK report.

Baseline-corrected serum copper concentrations that are less than or equal to zero will be treated as zero for the calculation of summary statistics and in the noncompartmental analysis.

8.5 Imputation of Missing Data

No imputation of missing data is planned at this time. Any missing data imputations will be detailed in the final PK report.

8.6 Data Exclusions

No data exclusions are planned at this time. Any exclusions will be detailed in the final PK report.

8.7 Significant Figures

Concentration data and PK parameters will be generally reported to 3 significant figures. All associated summary statistics for these parameters will also be reported to 3 significant figures, except for N which will be reported as an integer. Discrete time parameters (such as Tmax) and associated summary statistics will be reported to 2 decimal places.

9. PART C – PHARMACOKINETIC AND STATISTICAL ANALYSES DURING EXTENSION PHASE

9.1 Noncompartmental Pharmacokinetic Analysis and Descriptive Statistics

All final PK analysis and reporting for the VeraCept data for the combined Treatment Comparison and Extension Phases will be performed according to applicable Nuventra standard operating procedures and protocol specifications as outlined in Section 8. Analyses of Extension Phase data will be conducted at sponsor-directed intervals (e.g., after a 2-year data cut) as well as at the end of the 5-year study.

PK parameters for uncorrected and baseline-corrected serum copper will be calculated as described in Table 9-2.

Table 9-1. Pharmacokinetic Parameters

Parameter	Description
Combined Data from Treatment Comparison and Extension Phases (Treatment A, VeraCept IUD only)	
Cmax	Maximum observed concentration, observed by inspection of individual study participant serum concentration-time plots
Tmax	Time of maximum observed concentration, obtained directly from the observed concentration-time data
Cmean	Mean total serum copper concentration of samples collected after Day 1

Note that the abbreviations and definitions listed above may differ slightly from the protocol in the phrasing; however, the equations and methods used to generate these parameters do not differ from the protocol.

9.2 Statistical Analyses

Following Day 56 (study Day 57/Extension Phase), serum copper concentrations will only be collected for the VeraCept treatment group. These data will be listed, and additional statistical analyses or data presentations may be performed as appropriate.

10. SAFETY DATA SUMMARY AND REPORTING DURING TREATMENT COMPARISON PHASE AND TREATMENT EXTENSION PHASE

During the study, the investigator or study site personnel will be responsible for querying and recording AEs and serious adverse events (SAEs), as detailed below. For the sponsor to fulfill safety assessment obligations, the investigator will have to report all SAEs to the study sponsor, whether or not they result from study participation, within 24 hours of learning of the event.

10.1 Definition of an Adverse Event

The protocol defines an AE as any untoward medical occurrence in a clinical investigation subject administered an investigational product and which does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Any AE (i.e., a new event or an exacerbation of a pre-existing condition) with an onset from the day of informed consent/assent through Study Exit will be recorded as an AE on the electronic Case Report Form. All AEs will have to be recorded regardless of the severity or relationship to study drug. Investigators will also report all AEs that result in expulsion or removal of the investigational product being studied, whether serious or non-serious.

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

10.2 Definition of a Serious Adverse Event

The protocol defines an SAE as 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.

Examples of SAEs include but are not limited to: intensive treatment in an emergency room, hospitalization for any reason, and extensive treatment at home for an AE. An ectopic pregnancy is considered an SAE.

10.3 Adverse Events of Specific Interest

AEs of particular clinical importance, other than SAEs will be classified as adverse events of specific interest (AESIs). For this study, AESIs will refer to reports of pain during insertion, pelvic infection (pelvic inflammatory disease 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 Data and Safety Monitoring Board meetings and for the Clinical Study Report. For each AESI, a narrative will be written and included in the Clinical Study Report.

10.4 Safety Analyses

Safety analyses will be recorded and analyzed for the ParaGard subjects up to Day 57 and up to 5 years for the VeraCept subjects. Further information about safety analyses can be found in the safety analysis plan authored by Synteract.

11. TABLES, FIGURES, LISTINGS, AND APPENDICES

The following is a proposed listing of tables, figures, listings, and appendices to be generated with the interim and final PK analyses and included in the final PK report. Additional tables, figures, listings, and appendices may be generated, as necessary, to fully characterize and explore the available PK data, and captions/titles may be modified to accurately reflect the contents. Only those tables, figures, listings, and appendices supported by sufficient PK data will be generated.

The list of planned safety data summary tables and listings for the safety data can be found in the safety analysis plan authored by Synteract. The safety data summary tables and listings and the resulting safety conclusions will be generated by Synteract and will be included in the final PK report.

11.1 List of Tables

11.1.1 In-text Tables

Caption	Comments	Notes for Programming
Subject Demographics by Phase and Treatment Group	Separate columns for Treatment Comparison and Extension Phases, with the former presenting data for VeraCept, ParaGard, and Overall Extension Phase column will present data for VeraCept subjects from the Treatment Comparison Phase who will continue in the Extension Phase	Shortcut: DT Previous Shortcut: DT1 S.VAR: Phase + Treatment Group Update previous Day 57 table "Subject Demographics by Treatment Group"
Summary of Noncompartmental Pharmacokinetic Parameters for Serum Copper by Treatment for the Treatment Comparison Phase	Include Cmax, Tmax, Cmean, AUC0-56 Treatment Comparison Phase only	Shortcut: PSf Previous Shortcut: PS2 S.VAR: Treatment
Summary of Noncompartmental Pharmacokinetic Parameters for Serum Copper for the Combined Treatment Comparison Phase and Extension Phase	Include Cmean, Cmax, and Tmax Combined data from Treatment Comparison and Extension Phases, VeraCept data only	Shortcut: PSf Previous Shortcut: PS2 S.VAR: Treatment
Summary of Noncompartmental Pharmacokinetic Parameters for	Include Cmax, Tmax, Cmean, AUC0-56	Shortcut: PSf

Caption	Comments	Notes for Programming
Baseline-Corrected Serum Copper by Treatment for the Treatment Comparison Phase	Treatment Comparison Phase only	Previous Shortcut: PS2 S.VAR: Treatment
Summary of Noncompartmental Pharmacokinetic Parameters for Baseline-Corrected Serum Copper for the Combined Treatment Comparison Phase and Extension Phase	Include Cmean, Cmax, and Tmax Combined data from Treatment Comparison and Extension Phases, VeraCept data only	Shortcut: PSf Previous Shortcut: PS2 S.VAR: Treatment
Results from Statistical Assessment of Relative Bioavailability Based on Serum Copper Pharmacokinetic Parameters for the Treatment Comparison Phase	Cmax, Cmean, and AUC0-56 to be assessed Treatment Comparison Phase only	Shortcut: LT Previous Shortcut: LT1 S.VAR: None
Results from Statistical Assessment of Relative Bioavailability Based on Baseline-Corrected Serum Copper Pharmacokinetic Parameters for the Treatment Comparison Phase	Cmax, Cmean, and AUC0-56 to be assessed Treatment Comparison Phase only	Shortcut: LT Previous Shortcut: LT1 S.VAR: None
Summary of Shifts from Baseline in Serum Copper Concentrations by Phase and Treatment Group	Separate columns for Treatment Comparison and Extension Phases, with the former presenting data for VeraCept, ParaGard, and Overall Extension Phase column will present data for VeraCept subjects from the Treatment Comparison Phase who will continue in the Extension Phase	Shortcut: Custom Previous Shortcut: Custom S.VAR: Phase + Treatment Group Update previous Day 57 table "Summary of Shifts from Baseline in Serum Copper Concentrations by Treatment Group and Overall"

11.1.2 Post-text Tables

Caption	Comments	Notes for Programming
Summary of Subject Disposition by Phase and Treatment Group	Separate columns for Treatment Comparison and Extension Phases, with the former presenting data for VeraCept, ParaGard, and Overall Extension Phase column will present data for VeraCept subjects from the Treatment Comparison Phase who will continue in the Extension Phase	Shortcut: Custom Previous Shortcut: Custom S.VAR: Phase + Treatment Group Update previous Day 57 table "Summary of Subject Disposition"
Subject Accountability Table for the Treatment Comparison Phase	Treatment Comparison Phase only	Shortcut: AC Previous Shortcut: AC1 S.VAR: Treatment
Serum Copper Concentrations (ng/mL) and Summary Statistics by Sample Collection Time and Treatment for the Treatment Comparison Phase	Treatment Comparison Phase only	Shortcut: CT Previous Shortcut: CT1 S.VAR: Treatment
Baseline-Corrected Serum Copper Concentrations (ng/mL) and Summary Statistics by Sample Collection Time and Treatment for the Treatment Comparison Phase	Treatment Comparison Phase only	Shortcut: CT Previous Shortcut: CT1 S.VAR: Treatment
Noncompartmental Pharmacokinetic Parameters for Serum Copper and Summary Statistics by Treatment for the Treatment Comparison Phase	Treatment Comparison Phase only	Shortcut: PT Previous Shortcut: PT1 S.VAR: Treatment
Noncompartmental Pharmacokinetic Parameters for Baseline-Corrected Serum Copper and Summary Statistics by Treatment for the Treatment Comparison Phase	Treatment Comparison Phase only	Shortcut: PT Previous Shortcut: PT1 S.VAR: Treatment

Subject Accountability Table for the Extension Phase	Include Treatment column to indicate all data belongs to VeraCept Treatment Group	Shortcut: AC Previous Shortcut: AC1 S.VAR: Treatment
Serum Copper Concentrations (ng/mL) and Summary Statistics by Sample Collection Time for the Extension Phase	Include Treatment column to indicate all concentrations belong to VeraCept Treatment Group	Shortcut: CT Previous Shortcut: CT1 S.VAR: Treatment
Baseline-Corrected Serum Copper Concentrations (ng/mL) and Summary Statistics by Sample Collection Time for the Extension Phase	Include Treatment column to indicate all concentrations belong to VeraCept Treatment Group	Shortcut: CT Previous Shortcut: CT1 S.VAR: Treatment
Noncompartmental Pharmacokinetic Parameters for Serum Copper and Summary Statistics for the Combined Treatment Comparison Phase and Extension Phase	Combined data from Treatment Comparison and Extension Phases, VeraCept data only	Shortcut: PT Previous Shortcut: PT1 S.VAR: Treatment
Noncompartmental Pharmacokinetic Parameters for Baseline-Corrected Serum Copper and Summary Statistics for the Combined Treatment Comparison Phase and Extension Phase	Combined data from Treatment Comparison and Extension Phases, VeraCept data only	Shortcut: PT Previous Shortcut: PT1 S.VAR: Treatment

11.2 List of Figures

11.2.1 In-text Figures

Caption	**Comments**	**Notes for Programming**
Mean Serum Copper Concentration vs Time Plot with Treatments Overlaid for the Treatment Comparison Phase (Linear Scale)	Separate line for each Treatment Treatment Comparison Phase only	Shortcut: SPO Previous Shortcut: SP1 S.VAR: Treatment

Mean Serum Copper Concentration vs Time Plot with Treatments Overlaid for the Treatment Comparison Phase (Semi-log Scale)	Separate line for each Treatment Treatment Comparison Phase only	Shortcut: SPO Previous Shortcut: SP1 S.VAR: Treatment
Mean Serum Copper Concentration vs Time Plot for the Combined Treatment Comparison Phase and Extension Phase (Linear Scale)	Combined data from Treatment Comparison and Extension Phases, VeraCept data only	Shortcut: SPO Previous Shortcut: SP1 S.VAR: Treatment
Mean Serum Copper Concentration vs Time Plot for the Combined Treatment Comparison Phase and Extension Phase (Semi-log Scale)	Combined data from Treatment Comparison and Extension Phases, VeraCept data only	Shortcut: SPO Previous Shortcut: SP1 S.VAR: Treatment

11.2.2 Post-text Figures

Caption	**Comments**	**Notes for Programming**
Mean Baseline-Corrected Serum Copper Concentration vs Time Plot with Treatments Overlaid for the Treatment Comparison Phase (Linear and Semi-log Scale)	Separate line for each Treatment Treatment Comparison Phase only	Shortcut: SPO Previous Shortcut: SP1 S.VAR: Treatment
Overlay of Individual Subject Serum Copper Concentration vs Time Plot by Treatment for the Treatment Comparison Phase (Linear and Semi-log Scale)	Treatment Comparison Phase only	Shortcut: IOP Previous Shortcut: IO1 S.VAR: Treatment
Overlay of Individual Subject Baseline-Corrected Serum Copper Concentration vs Time Plot by Treatment for the Treatment Comparison Phase (Linear and Semi-log Scale)	Treatment Comparison Phase only	Shortcut: IOP Previous Shortcut: IO1 S.VAR: Treatment
Boxplot Comparing Serum Copper Cmax by Treatment for	Treatment Comparison Phase only	Shortcut: BP

the Treatment Comparison Phase (Linear Scale)		Previous Shortcut: BP1 S.VAR: Treatment
Boxplot Comparing Baseline-Corrected Serum Copper Cmax by Treatment for the Treatment Comparison Phase (Linear Scale)	Treatment Comparison Phase only	Shortcut: BP Previous Shortcut: BP1 S.VAR: Treatment
Boxplot Comparing Serum Copper Cmean by Treatment for the Treatment Comparison Phase (Linear Scale)	Treatment Comparison Phase only	Shortcut: BP Previous Shortcut: BP1 S.VAR: Treatment
Boxplot Comparing Baseline-Corrected Serum Copper Cmean by Treatment for the Treatment Comparison Phase (Linear Scale)	Treatment Comparison Phase only	Shortcut: BP Previous Shortcut: BP1 S.VAR: Treatment
Boxplot Comparing Serum Copper AUC0-56 Days by Treatment for the Treatment Comparison Phase (Linear Scale)	Treatment Comparison Phase only	Shortcut: BP Previous Shortcut: BP1 S.VAR: Treatment
Boxplot Comparing Baseline-Corrected Serum Copper AUC0-56 Days by Treatment for the Treatment Comparison Phase (Linear Scale)	Treatment Comparison Phase only	Shortcut: BP Previous Shortcut: BP1 S.VAR: Treatment
Mean Baseline-Corrected Serum Copper Concentration vs Time Plot for the Combined Treatment Comparison Phase and Extension Phase (Linear and Semi-log Scale)	Combined data from Treatment Comparison and Extension Phases, VeraCept data only	Shortcut: SPO Previous Shortcut: SP1 S.VAR: Treatment
Overlay of Individual Subject Serum Copper Concentration vs Time Plot for the Combined Treatment Comparison Phase	Combined data from Treatment Comparison and Extension Phases, VeraCept data only	Shortcut: IOP Previous Shortcut: IO1 S.VAR: Treatment

and Extension Phase (Linear and Semi-log Scale)		
Overlay of Individual Subject Baseline-Corrected Serum Copper Concentration vs Time Plot for the Combined Treatment Comparison Phase and Extension Phase (Linear and Semi-log Scale)	Combined data from Treatment Comparison and Extension Phases, VeraCept data only	Shortcut: IOP Previous Shortcut: IO1 S.VAR: Treatment

11.3 Listings

Caption	**Comments**	**Notes for Programming**
Listing of Individual Subject Demographic Data	Treatment Comparison and Extension Phases Include Phase column	Shortcut: LT Previous Shortcut: LT1 S.VAR: None Update the previous Day 57 listing "Listing of Individual Subject Demographic Data"
Listing of Serum Copper Concentration Time Data for Noncompartmental Analysis by Phase and Treatment	Treatment Comparison and Extension Phases Include Phase column	Shortcut: LT Previous Shortcut: LT1 S.VAR: None Update the previous Day 57 listing "Listing of Serum Copper Concentration Time Data for Noncompartmental Analysis by Treatment"
Listing of Baseline-Corrected Serum Copper Concentration Time Data for Noncompartmental Analysis by Phase and Treatment	Treatment Comparison and Extension Phases Include Phase column	Shortcut: LT Previous Shortcut: LT1 S.VAR: None

		Update the previous Day 57 listing "Listing of Baseline-Corrected Serum Copper Concentration Time Data for Noncompartmental Analysis by Treatment"

11.4 Appendix Figures

Caption	Comments	Notes for Programming
Individual Subject Serum Copper Concentration vs Time Plot for the Treatment Comparison Phase (Linear Scale)	Separate lines for uncorrected and baseline-corrected concentrations within each subject on the same plot Separate plot for each subject Treatment Comparison Phase only	Shortcut: IP Previous Shortcut: IP1 S.VAR: Treatment + Concentration Type (i.e., Uncorrected or Baseline-Corrected)
Individual Subject Serum Copper Concentration vs Time Plot for the Combined Treatment Comparison Phase and Extension Phase (Linear Scale)	Separate lines for uncorrected and baseline-corrected concentrations within each subject on the same plot Separate plot for each subject Combined data from Treatment Comparison and Extension Phases, VeraCept data only	Shortcut: IP Previous Shortcut: IP1 S.VAR: Treatment + Concentration Type (i.e., Uncorrected or Baseline-Corrected)

SAFETY STATISTICAL ANALYSIS PLAN

A Randomized, Single-Blind, Comparative Bioavailability Study to Assess the Pharmacokinetic Properties of VeraCept® Intrauterine vs ParaGard® in Healthy, Post-Menarcheal Women

Protocol Number:	CMDOC-0045
Protocol Version / Date:	Version 2.0 / 03JUL2019
Sponsor:	Sebela Women's Health Inc. 645 Hembree Parkway, Suite I Roswell, GA 30076
SAP Version:	Version 2
SAP Date:	20SEP2024
Previous Version:	Version 1/ 01NOV2021

CONFIDENTIAL

SAFETY STATISTICAL ANALYSIS PLAN

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Approvals

Syneos Health Approval

[redacted]

Sebela Women's Health Inc. Approval

[redacted]

/25/2024

Name, Title Sponsor Contact		Signature	Date (DD-Mmm-YYYY)

[redacted]		23/2024
Name, Title Sponsor Contact		Signature Date (DD-Mmm-YYYY)
[redacted]		Signed by: /23/2024
Name, Title Sponsor Contact		Signature Date (DD-Mmm-YYYY)

TABLE OF CONTENTS

REVISION HISTORY

Version	Date	Reason for Revision
2.0	20SEPT2024	• Cross referenced shells and updated sections to match what is currently being produced. o Added Incidence of TEAEs by SOC and PT by closest relationship to study device for the Safety population will be presented. o Updated AEs to TEAEs where appropriate o Included BMI in vital signs section o Added Pelvic Examination and Transvaginal Ultrasound

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AESI	adverse event of specific interest
AUC0-56 days	area under the concentration-time curve from study time 0 (study Day 1) to Day 56 (study Day 57)
BE	bioequivalence
BMI	body mass index
CHG	change from baseline
Cmax	maximum observed concentration
Cmean	mean total serum copper concentration of samples collected after Day 1 (Days 2-56)
CRF	case report form
CSR	clinical study report
EP	evaluable for pregnancy
EVTDY	Study Day of Event
EXDUR	Exposure Duration in Days
ICH	International Council for Harmonization
INT	Integer
ITT	intent to treat
IUD	intrauterine device
MedDRA	Medical Dictionary for Regulatory Activities
NCYCC	Number of Completed Cycles
NCYCEV	Number of Evaluable Cycles
NCYCF	Exposure Duration in Cycles
NCYCR	Number Relevant Cycles
PENDY	Study Day of Period End
PK	pharmacokinetic
PSTDY	Study Day of Period Start
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 Women's Health Inc. (Sebela) study titled "A Randomized, Single-Blind, Comparative Bioavailability Study to Assess the Pharmacokinetic Properties of VeraCept® Intrauterine vs Paragard® in Healthy, Post-Menarcheal Women," protocol number CMDOC-0045, version 2.0, dated July 03, 2019. 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). This analysis plan is specifically for safety analyses as the pharmacokinetic (PK) analyses are covered under a separate PK Analysis Plan.

Syneos Health, will write the clinical study report (CSR) following the guidelines in the ICH E3 document.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

The primary objective of the study is to assess the relative bioavailability of observed systemic copper from VeraCept intrauterine device (IUD) versus Paragard IUD based on maximum observed concentration (Cmax), mean copper concentration of samples collected after Day 1 (Days 2-56) (Cmean), and area under the concentration-time curve from study time 0 (study Day 1) to Day 56 (study Day 57) (AUC0-56 days).

The secondary objectives of the study are:

- To assess the relative bioavailability of baseline-corrected total serum copper from the VeraCept IUD versus Paragard based on Cmax, Cmean, and AUC0-56 days.
- To assess the total serum copper levels within each treatment relative to the normal range (49 to 184 µg/dL) [1].
- To assess the long-term stability of copper levels following insertion of the VeraCept IUD.

2.2 Endpoints

The primary endpoint is the mean total serum concentration, Cmax, and AUC0-56 days for observed copper for each treatment.

Secondary endpoints include:

- Mean total serum concentration, Cmax, and AUC0-56 days for baseline-corrected copper for each treatment.
- Total serum copper concentrations, Cmax, and AUC0-56 days for baseline-corrected copper for each treatment.
- Mean total serum copper concentrations for observed and baseline-adjusted copper for Treatment A (VeraCept IUD only) over 5 years.

3 STUDY DESIGN AND INVESTIGATIONAL PLAN

This parallel, single-blind study is designed to evaluate the comparative bioavailability of systemic copper exposure after insertion of VeraCept IUD versus Paragard in post-menarcheal women. Up to 40 subjects will receive one of two treatments (A or B) as described below:

- Treatment A (N=20): VeraCept® IUD, test (referred to as VeraCept)
- Treatment B (N=20): Paragard® IUD, reference (referred to as Paragard)

Subjects will be screened within 60 days prior to the first insertion of study device, and blood samples will be collected within 28 days from first insertion of study device at two visits within this screening period to establish baseline copper concentrations. At least 24 hours should separate each baseline sample. On Day 1 of each treatment period, PK, safety, and baseline assessments will be collected prior to IUD insertion. Subjects will return to the clinic at 48 hours post-IUD insertion (Day 3 [±24 hours]) and on Days 8 (±1 day), 15 (±1 day), 22 (±1 day), 29 (±1 day), and 57 (±3 days) for blood collections that will be used to measure total serum copper concentrations.

On Day 57, Paragard subjects will exit the study and may continue Paragard use per standard clinical care. VeraCept subjects will continue in the extension phase of the study that is intended to assess the long-term stability of serum copper concentrations up to 5 years and to monitor safety. During the first 3 years, subjects will return to the clinic every 6 months for clinical assessments and blood collections that will be used to measure total serum concentrations. Following Year 3, subjects will return annually up to Year 5. During the extension phase, PK collections may occur anytime within 30 days of the planned collection time. Subjects prematurely discontinuing the study should follow the procedures specified in Section 6.1.7 of the protocol, Early Discontinuation Visit. Additional follow-up visits may be scheduled, as needed, if a subject has an ongoing significant adverse event (AE) and/or a clinically significant laboratory abnormality.

3.1 Study Schedule of Assessments

A schedule of assessments is provided in Table 1.

3.2 Determination of Sample Size

The assumption is that there is no additional systemic exposure of copper when using the IUD. The primary analysis will use uncorrected total serum copper parameters (Cmax, Cmean, and AUC0-56 days). A secondary analysis will be conducted using baseline-corrected total serum copper parameters (Cmax, Cmean, and AUC0-56 days).

No formal hypothesis testing is being done for the analysis using Cmax and Cmean; therefore, a precision approach will be taken with boundaries chosen to reflect typical bioequivalence (BE) boundaries in the ln scale (±22%). Assuming a normal range of 49 to 184 µg/dL, an estimate of the normal (mean) value could be close to 110-120 µg/dL. A comparable boundary would be ±22. This estimated mean with the added half-width still falls well within the normal range. No formal hypothesis testing is being done for the analysis using AUC0-56 day; therefore, a precision approach will be taken with boundaries chosen to reflect typical BE boundaries in the ln scale (±22%). AUC values will be ln transformed.

For a two-sided 90% confidence interval for a two-sample normal mean difference, assuming a common standard deviation of 25, a sample size of 12 per group is required to obtain a maximum half-width of 22 μg/dL with a conditional probability of at least 0.90 given that the interval contains the true mean difference. The actual probability is 0.95. Assuming a maximum unevaluable rate of 40%, up to 20 subjects will be enrolled in each group. Replacement subjects may be enrolled as needed to ensure that at least 24 evaluable subjects complete the study.

3.3 Interim Analyses

The primary analysis for this study is covered under the PK SAP and covers the treatment comparison phase up to Day 57 (VeraCept vs Paragard) and the VeraCept only treatment extension phase that took place after Day 57 up to 5 years. Safety analyses will be performed for the treatment comparison phase up to Day 57 and for VeraCept only in the treatment extension phase after the last subject completes Year 3, (along with corresponding 120-day Safety updates for years 3 -5) and after database lock when all subjects complete Year 5.

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 device insertion attempts, which could be on different dates. The following 2 study reference dates will be defined to meet the analysis requirements specified in 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 purposes, 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 Study Data Tabulation Model (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 latter result will be used for the summary measure. All measures may not be used in the data summaries (e.g., 2 vital signs measures within the same analysis visit window), but all measurements will appear in the datasets and listings.

Table 4.1.4.1 Analysis Windows:

Scheduled Visit (Subject Visit Window)	Analysis Visit	Analysis Window Target Day	Analysis Window	
			Lower Bound	Upper Bound
Visit 1/Screening	Baseline	1	N/A	1
Visit 2 (Day 1)				
Visit 3 (Day 3± 24 hours)	Day 3	3	2	5
Visit 4 (Day 8± 1 day)	Day 8	8	6	11
Visit 5 (Day 15± 1 day)	Day 15	15	12	18
Visit 6 (Day 22± 1 day)	Day 22	22	19	25
Visit 7 (Day 29± 1 day)	Day 29	29	26	43
Visit 8 (Day 57± 3 days)	Day 57	57	44	120
Visit 9 (Month 6± 30 days)	Month 6	182	121	273
Visit 10 (Month 12± 30 days)	Month 12	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	1278
Visit 14 (Month 48± 1 month)	Month 48	1460	1279	1642
Visit 16 (Month 60± 1 month)	Month 60	1825	1643	N/A

4.1.5 Exposure Periods

The first exposure cycle starts on Day 1 of successful study device 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, D, E, or F

=NCYCC, otherwise.

Number of Evaluable Cycles (NCYCEV) =NCYCR

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 device 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

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 Adverse Event

4.1.7.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation where a subject has been administered an investigational product and which does not necessarily 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 insertion of the device.

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

4.1.7.2 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 device; or
- Important medical events that may not result in death, be immediately life threatening, or require hospitalization. Events may also 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.

4.1.7.3 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 pain during insertion, pelvic infection (e.g., pelvic inflammatory disease or endometritis), dysmenorrhea, abdominal pain, expulsion, and uterine perforation. AESIs will be identified and assessed by the Medical Monitor during the ongoing monitoring of safety data during the trial, and for the CSR. For each AESI, a narrative may be written and included in the CSR.

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

A missing relationship will be imputed as “related”.

4.1.7.5 Adverse Events Related to Study Procedures

Adverse events that occur during the study device placement procedure or removal procedure will be reported on the AE case report form and will be assigned one of the relationships noted in Section 4.1.7.4 by the study Investigator. Any missing relationships will be imputed as “related to the study device placement procedure”.

4.1.7.6 Adverse Event Severity

The study investigator will assess the severity of the AE, and severity will be assigned one of the following values: Mild, Moderate, Severe, Life-threatening, or Fatal.

For analysis purposes, Fatal or Life-threatening will be coded as Severe; missing severity will be imputed as Severe.

4.1.8 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 or 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, and 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

- **Intent to Treat (ITT):**

  All subjects randomized to the study. This will include subjects who underwent the study device placement procedure, regardless of whether the study device was successfully placed or not.

- **Safety:**

  All subjects who undergo a successful study device placement procedure.

- **Evaluable for Pregnancy (EP):**

  Safety subjects who had VeraCept or Paragard placed successfully and meet requirements 1, 2 and 3 as follows.

  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.

  Subjects with major protocol violations that are deemed to have had a material impact on the assessment of the pearl index will be excluded from the EP analysis population.

Exclusions based on major protocol deviations will be reviewed and approved by Sebela and its designee.

4.3 Analysis Population Subgroups

No subgroups will be analyzed.

4.4 General Data Presentation Plan

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

Unless otherwise specified, the table summary for the main study will display the following columns:

Analysis Population	**Table Display Columns**		
ITT	VeraCept	Paragard	Overall
Safety	VeraCept	Paragard	Overall
EP	VeraCept		

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).

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, or safety data unless stated otherwise for a specific parameter in the SAP. Point estimates will be presented with their 95% confidence intervals (CIs) where appropriate.

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, the worst-case scenario will be applied for the start date/time of an AE or medication that is partially or completely missing. 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.

A disposition table will report the following:

- The number and percentage of subjects in each analysis population
- The number and percentage of subjects who discontinued the study prior to Day 57, including the reasons for discontinuation
- The number and percentage of subjects who completed Day 57

- The number and percentage of subjects who discontinued the study after Day 57 but prior to 1 year of use, including the reasons for discontinuation
- The number and percentage of subjects who complete 1 year of use
- The number and percentage of subjects who discontinued the study after 1 year of use but prior to 2 years of use, including the reasons for discontinuation
- The number and percentage of subjects who completed 2 years of use
- The number and percentage of subjects who discontinued the study after 2 years of use but prior to 3 years of use, including the reasons for discontinuation
- The number and percentage of subjects who completed 3 years of use
- The number and percentage of subjects who discontinued the study after 3 years of use but prior to 4 years of use, including the reasons for discontinuation
- The number and percentage of subjects who completed 4 years of use
- The number and percentage of subjects who discontinued the study after 4 years of use but prior to 5 years of use, including the reasons for discontinuation
- The number and percentage of subjects who completed the study (5 years of use)

Listings will be generated for the following:

- Subject's disposition
- Subject's membership in each analysis population and reason for exclusion from each analysis population

4.6 Protocol Deviations

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

4.7 Baseline Demographics and Characteristics

Baseline demographics will be summarized for the ITT, EP, and Safety 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:

- Age (years) at enrollment
- Age group at enrollment (≤35 years old, 36-45 years old)
- Ethnicity
- Race
- Marital status at enrollment
- Weight (kg) at enrollment

- Height (cm) at enrollment
- Body mass index (BMI) (kg/m^2) at enrollment
- BMI group (<30 kg/m^2, ≥ 30 kg/m^2) at enrollment

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 body system and report term.

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

4.7.3 Baseline 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.

Physical examination results indicating clinically significant abnormalities will be presented in a data listing.

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 also 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 also be presented in a data listing.

4.7.6 Cervical Cytology

Cervical cytology test results will be summarized in the 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. These medications will be recorded on CRF page and coded using the WHO Drug dictionary. The CSR will include the version number of the WHO Drug dictionary. Prior medications are defined as those taken by the subject prior to the study device placement. Concomitant medications are defined as those taken by the subject from the date of the study device 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 according to anatomical therapeutic chemical classification Level 4 and generic term for the ITT population.

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

4.8 Pearl Index Analysis

The pearl index will be utilized to measure contraceptive efficacy through 5 years of use and will be analyzed using the Pearl Index with a 95% CI for women in the EP population. A separate summary of the Pearl Index in the EP Population through Day 57 will also be provided.

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, 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.

x =sum of PREGNANCY

E =number of Evaluable Cycles (NCYCEV)

Pearl Index point estimates and 95% CIs will be calculated for Day 57, Years 1, 2, 3, 4, 5, Years 1-2, Years 1-3, Years 1-4, and for Years 1-5 separately.

4.9 Study Device Placement and Exposure

Study device placement and removal data will be summarized for the ITT and Safety population, respectively including the number of relevant and evaluable cycles with device use for subjects randomized to VeraCept. The study device placement and removal data will be presented in the listings.

4.9.1.1 Study Device Placement

The following parameters will be reported in the table for study device 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
- Had medication during either attempt
- Required mechanical dilation in either attempt
- Number of cycles with device in place for Years 1, 2, 3, 4, 5 separately

4.9.1.2 Study Device Expulsion/Removal

The following parameters will be reported in the table for Years 1, 2, 3, 4, and 5 separately:

Number (%) of subjects who had study device removal

Number (%) of subjects who had study device expulsion

Number (%) of subjects with device expelled prior to the visit along with corresponding expulsion status (partial or complete)

Number (%) of subjects who had removal accomplished by pulling the strings without difficulty

Number (%) of subjects with each reason for difficulty of removal

Number (%) of subjects with medication given during the procedure.

4.10 Multiplicity Adjustment

There is no formal efficacy analysis contained in this SAP, and there is no need for multiplicity adjustment for type I error α.

4.11 Safety and Tolerability

Adverse events will be coded and classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. The summaries of AEs will be limited to TEAEs. Number (%) of subjects reporting AEs and SAEs will be summarized for the Safety population.

4.11.1 Brief Summary of Adverse Events

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

- AE
- AE related to study device
- AE related to study device placement/removal procedure
- SAE
- SAE related to study device placement/removal procedure
- AE leading to study device removal
- AE leading to study discontinuation
- AE leading to Death

4.11.2 Adverse Events by System Organ Class and Preferred Term

The incidence of Treatment-Emergent Adverse Events (TEAE) and SAEs 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 TEAEs by SOC and PT by maximum severity for the Safety population will be presented.

Incidence of TEAEs by SOC and PT by closest relationship to study device for the Safety population will be presented.

The incidence of TEAEs by SOC and PT by closest relationship to drug placement/removal procedure for the Safety population will be presented.

The incidence of Treatment-Emergent SAEs by SOC and PT by closest relationship to drug placement/removal procedure for the Safety population will be presented.

Incidence of TEAEs experienced by at least 10% of subjects by SOC and PT for the Safety population

Incidence of AESIs (pain during insertion, pelvic infection (Pelvic Inflammatory Disease or endometritis), expulsions and uterine perforations), which includes the following MedDRA preferred terms: abdominal pain, abdominal pain lower, abdominal pain upper, pelvic inflammatory disease, procedural pain, device expulsion, dysmenorrhea following IDU placement, dysmenorrhea-post-procedural, embedded device, insertion pain, intermittent dysmenorrhea, post procedural dysmenorrhea, uterine perforation, worsening of dysmenorrhea, endometritis, post procedural discomfort, pelvic discomfort and pelvic pain will be summarized for the Safety population.

Incidence of Allergy-Related AEs, based on Medical Monitor review, will be summarized by PT and relationship to study device will be presented in the Safety population.

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

Narratives of deaths, SAEs, AESIs, pregnancies, allergic reactions occurring within 30 days of insertion and/or related to VeraCept will be provided in the relevant section of the CSR.

4.11.4 Adverse Events Listings

A complete subject listing of all AEs will be provided in Appendix 16.2 in the CSR. 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 device, duration of the AE, whether serious or not, severity, relationship to study device, 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 device, AEs related to study device placement/removal procedure, AEs leading to death, AEs leading to study device removal, AESIs, Allergy-Related AEs and AEs as primary reason for exiting study will be provided.

4.11.5 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.

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, defined as the date the subject was deemed lost to follow-up as entered on the Study Exit Status CRF page.
- Those with VeraCept still in place for protection at the end of exposure period will be censored at the end of exposure period.

4.11.6 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)
- BMI (kg/m^2)
- BMI (underweight, normal, overweight, obese)

Vital signs, weight, and BMI will be included in a data listing.

4.11.7 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.

4.11.8 Physical examination results indicating significant abnormalities will be presented in a data listing. Pregnancy Results

All pregnancy testing data will be presented in the listings.

Pregnant subjects with clinical outcome data including infant abnormalities will be presented in the listings.

4.11.9 Pelvic Examination and Transvaginal Ultrasound

All pelvic examination and transvaginal ultrasound data will be presented in a data listing.

5 CHANGES FROM PROTOCOL

The pearl index based on safety cycles was added as a measure of the contraceptive efficacy. The reference product labeling was updated after the study initiated and removed capitalization of the G.

6 REFERENCES

1. Salwen, M.J., *Vitamins and Trace Elements* 23 ed. Henry's Clinical Diagnosis and Management by Laboratory Methods, 23rd Edition. 2017, St. Louis, Missouri: Elsevier Health Sciences. 1700.

Table 1: Study Schedule of Assessments

Visit	Screening	Enrollment/IUD Placement	Clinic PK visits		Clinic PK visits (VeraCept Subjects ONLY)	Month 60 OR Exit Visit
Day	**Day -28 to 1**	**Day 1**	**Day 3 (±24 hrs)**	**Days 8, 15, 22, 29 (±1 day) Day 57[6] (±3 days)**	**Months 6, 12, 18, 24, 30, 36 and 48 (±30 days)**	**Month 60 (±30 days) OR Exit Visit**
Assessment of Eligibility	X	X				
Distribution of subject materials (if applicable)	X					
Informed Consent/Assent/PHI and Bill of Rights	X					
Demographics and baseline characteristics	X					
Medical/surgical, gynecologic, and menstrual history	X					
Vital signs and weight	X	X	X	X	X	X
Height	X					
General physical exam	X					
Pelvic exam (string check if post IUD insertion)	X	X[1]		X	X	X
Cervical cytology	X					
Cervical infection tests	X[2,3]					
Transvaginal, ultrasound, only if clinically indicated		X		X	X	X
Pregnancy test – urine	X	X				X
Prior and concurrent medication	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
IUD placement		X				
IUD removal						X[7]
Concomitant contraception		X				X
Subject education – need for contraception	X	X	X	X	X	X
Blood draw for PK analysis (serum copper sample)	X[4]	X[5]	X[5]	X[5]	X[5]	X[5]

Footnotes

1. Pelvic exam for IUD string check by palpation or visualization.

2. 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 IUD insertion, the subject should be treated prior to IUD placement. The subject may be inserted 7 days post-treatment. A cervical infection retest should be done 3-months post-IUD insertion to assure there is not a case of re-infection.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.

3. Insertion can occur without receipt of test results if there is no clinical evidence of infection. If, after IUD insertion, the screening cervical infection test results are positive, the subject should be treated. A cervical infection retest should be done 3 months post-treatment.

4. Subjects will be screened within 60 days prior to the first insertion of study drug, , and two blood samples will be collected within 28 days from Day 1, and at least 24 hours apart within this screening period (can be performed on Screening and Day 1 visit prior to IUD insertion). to establish baseline copper concentrations.

5. On Day 1, collect blood samples for pharmacokinetic analysis prior to intrauterine insertion. On Day 3, collect samples 48 hours ±24 hours after IUD insertion. PK samples on Day 8, 15, 22, and 29 should be collected within 1 day of the planned collection day while Day 57 should be collected within 3 days of planned collection day, at approximately the same time as the Day 3, 48-hr ±1 day PK sample collection. Following the PK collections on Day 57, the PK samples should be collected within 30 days of the planned collection day.

6. Paragard subjects will have Exit Visit procedures completed on Day 57.

7. Paragard subjects may continue Paragard use per standard clinical care or have the device removed.