NCT03785366

STUDY PROTOCOL

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

DOCUMENT DATE: 03 Jul 2019

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

Study Number:	CMDOC-0045
Name of Investigational Product:	VeraCept Intrauterine Contraceptive
IND Number:	119743
Sponsor:	Sebela Pharmaceuticals, Inc. 645 Hembree Parkway, Suite I Roswell, GA 30076 Kevin Peters [redacted]
Study Phase:	Phase 3
National Principal Investigator:	David Turok, MD, MPH Associate Professor Obstetrics and Gynecology University of Utah School of Medicine
Medical Monitor:	Scott E. Eder, MD FACOG Medical Director, Synteract, Inc. [redacted]
Protocol Version:	2.0
Protocol Date:	03 Jul 2019

INVESTIGATOR PROTOCOL AGREEMENT

I have received a copy of Protocol Number CMDOC-0045, A Randomized, Single-Blind, Comparative Bioavailability Study to Assess the Pharmacokinetic Properties of VeraCept® Intrauterine Contraceptive vs ParaGard® in Healthy, Post-Menarcheal Women, Version 2.0 dated July 3, 2019 from Sebela. I agree to the conditions as set out in this protocol and fully accept that any change requires prior approval from Sebela. Additionally, I agree to carry out all terms of this protocol in accordance with International Conference on Harmonization (ICH) Guidelines, all applicable US Regulations (21 Code of Federal Regulations [CFR] parts 50, 54, 56 and 312) and Good Clinical Practice (GCP) Guidelines, as applicable. Finally, I will ensure that the investigational product will be used only as described in this protocol.

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

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

Investigator's Name (print)

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

REVISION HISTORY

Version	Date	Justification for Revision
1.0	08/10/ 2018	Initial version
2.0	07/03/2019	Administrative updates, update length of screening period, clarify baseline PK sample collection timelines, update inclusion/exclusion criteria, add post-pregnancy insertion timing guidelines, clarify double barrier method, add menstrual cup use information, clarify randomization procedure, clarify on-study pregnancy follow-up, add ParaGard Study Exit procedures, and update AE outcome definition

SYNOPSIS

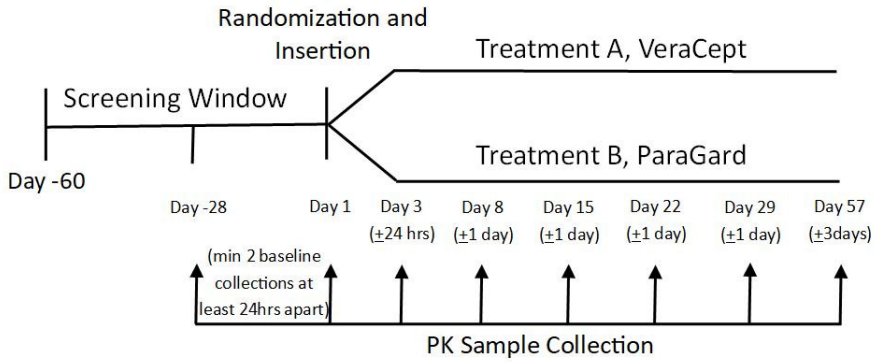
Name of Sponsor Company: Sebela Pharmaceuticals, Inc.

Name of Investigational Drug: VeraCept Intrauterine Contraceptive

Name of Active Ingredient: Copper

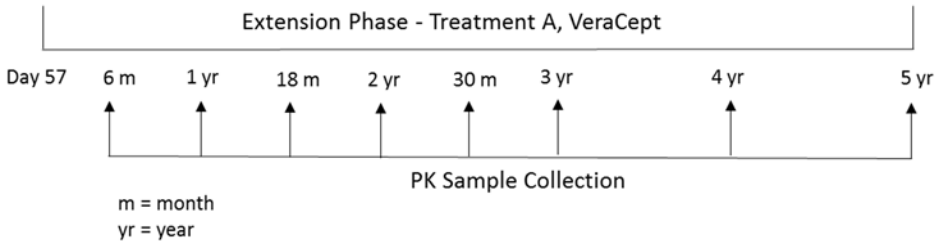
Title of Study	A Randomized, Single-Blind, Comparative Bioavailability Study to Assess the Pharmacokinetic Properties of VeraCept® Intrauterine Contraceptive vs ParaGard® in Healthy, Post-Menarcheal Women
Investigator(s) and Study Center(s)	Jeffrey Jensen, MD, MPH Oregon Health and Science University Women's Health Research Unit 3181 SW Sam Jackson Park Rd. Mail code: UHN70 Portland, OR 97239 Robin Kroll, MD Seattle Women's: Health, Research, Gynecology 3216 NE 45th Place, Suite 100 Seattle, WA 98105
Phase of Development	Phase 3
Study Objectives	The primary objective of this study is: • Assess the relative bioavailability of observed systemic copper from VeraCept versus ParaGard based on Cmax, Cmean, and AUC0-56 days The secondary objective of this study is: • 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). • To assess the long-term stability of copper levels following insertion of the VeraCept IUD
Study Design	This randomized, single-blind study is designed to evaluate the comparative bioavailability of systemic copper exposure after insertion of VeraCept vs ParaGard in post-menarcheal women. Up to 40 subjects from one or more sites 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)

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.

Extension Phase



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 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 assessment and blood collection for measurement of total serum concentrations. Following Year 3, subjects will return annually for up to Year 5. A schedule of the study procedures and assessments to be conducted for each subject is provided in the Time and Events Table (Appendix 1).

Study Rationale

In order to maximize the ability to detect a difference in copper exposure following insertion of VeraCept and ParaGard, this study has been designed to sample total serum copper concentrations for the first 60 days post-insertion. Copper release rates from copper IUDs have been shown to

	decrease over time with the predominant decrease in release rate occurring in the first 60 days [1]. The initial release rate of copper (the burst release) appears to be correlated with the exposed surface area of copper in the device. However, as the release rates decrease over time, the release rate of copper plateaus and appears to be less dependent on the exposed surface area of the device (Figure 1-1). Ion release testing (CTM-20141110-1) comparing VeraCept with Optima TCu380S, a commercial copper IUD with twice the exposed copper surface area, demonstrated that insertion of a copper IUD results in an initial burst of copper release followed by a steady decline in copper release rate which stabilizes by approximately 21 days of immersion (Figure 1-2). The highest average daily release rate was observed on day 1 at 1,600 ppb/day (~45 µg/day). From 21 to 60 days, the copper release rate remained relatively low and continued to decrease slightly from 278 ppb/day (~7.8 µg/day) on day 21 to 149 ppb/day (~4.2 µg/day) on day 60. According to Chantler et al. (1977) [1], the highest copper release rate for an IUD with a similar surface area to that of the marketed ParaGard IUD is approximately 3.2 µmol/day (~200 µg/day) while the corresponding value for VeraCept is approximately 1.2 µmol/day (~75 µg/day). By 60 days, the release rate for IUDs with exposed copper surface areas similar to that of ParaGard and VeraCept decreased to below 0.5 µmol/day or approximately 30 µg/day. Long-term studies of other copper IUDs have reported similar and even lower copper release rates [2, 3]. Average daily dietary intake of copper has been reported to be approximately 1.0 to 1.6 mg/day [4-6]. Based on the data described above, by 60 days following insertion, the copper released from these IUDs would represent less than 3% of daily dietary intake of copper. Given the small amount of copper released by the IUDs relative to the total daily intake of copper, it would be difficult to attribute serum copper concentrations to the IUD beyond this initial release period. Therefore, in order to maximize the potential to capture a difference in copper exposure following insertion of the IUD, the sampling schedule will focus on the first 60 days post-insertion (i.e. 48 hours post-insertion through Day 57). An extension phase following Day 57 for the VeraCept subjects will assess the long-term stability of copper levels following insertion of the VeraCept IUD up to 5 years.
Number of planned subjects	40 post-menarcheal women will be randomized (20 subjects per treatment), to obtain data from at least 12 evaluable subjects per treatment group. An evaluable subject is a subject who has pre-insertion copper concentrations within the normal range (49 to 184 µg/dL) [7], had an IUD placed successfully, and completes all scheduled PK sample collections without a protocol deviation or AEs that significantly impact the planned PK analyses to Day 57 and for VeraCept subjects continuing in the extension phase. Replacement subjects may be enrolled, as needed, to

	ensure that at least 24 evaluable subjects (12 subjects per treatment) complete the study.
Inclusion/Exclusion Criteria	**Inclusion Criteria** A subject will be eligible for inclusion in this study if they *meet all of the following criteria:* 1. Post-menarcheal, pre-menopausal females up to 45 years of age at the time of informed consent/assent and in good general health; 2. History of regular menstrual cycles defined as occurring every 21-35 days when not using hormones or prior to recent pregnancy or spontaneous or induced abortion; 3. Sexually active with a male partner who has not had a vasectomy; 4. Reasonably expect to have coitus at least once monthly during the study period; 5. In a mutually monogamous relationship of at least 3 months duration; 6. Seeking to avoid pregnancy for the duration of the study; 7. Willing to use the study drug as the sole form of contraception; 8. Willing to accept a risk of pregnancy; 9. Subjects must be in compliance with cervical cancer screening guidelines per the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines without evidence of disease. Subjects who are age 21-24 y/o, at time of informed consent, must have a normal papanicolaou test (Pap), atypical squamous cells of undetermined significance (ASC-US), or low-grade squamous intraepithelial lesion (LSIL). Subjects who are 25 or older at the time of informed consent with ASC-US results, must also have a negative high risk human papilloma virus (HPV) test result within the appropriate screen timeframe per American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines, and prior to the study IUD insertion. Alternatively, the subject must have had a colposcopy performed within the appropriate screen timeframe, and prior to the study IUD insertion that showed no evidence of dysplasia requiring treatment per ASCCP guidelines, or treatment was performed and follow-up at least 6 months after the treatment showed no evidence of disease by clinical evaluation; 10. Able and willing to comply with all study tests, procedures, assessment tools and follow-up; 11. Able and willing to provide and document informed consent and Authorization for Release of Protected Health Information (PHI). Unemancipated subjects under 18 years old must provide assent and

	have written parental consent documented on the consent form consistent with local legal requirements; 12. Plan to reside within a reasonable driving distance of a research site for the duration of the study. 13. Subject agrees not to self-remove VeraCept **Exclusion Criteria** *A subject will be excluded from participating in the study if any of the following conditions apply:* 1. Known or suspected pregnancy; or at risk for pregnancy from unprotected intercourse earlier in current cycle; 2. A previously inserted intrauterine device (IUD) that has not been removed by the time the study IUD is placed; 3. History of previous IUD complications, such as perforation, expulsion, or pregnancy with IUD in place; 4. Pain with current IUD; 5. Injection of hormonal contraceptive (e.g., Depo-Provera) within the last 10 months and has not had 2 normal menstrual cycles since the last injection; 6. Use of ParaGard IUD within the past 3 months 7. Planned use of any non-contraceptive estrogen, progesterone or testosterone any time during the 60 months of study participation; 8. Exclusively breastfeeding before return of menses; lactating women will be excluded unless they have had 2 normal menstrual periods prior to enrollment; 9. Unexplained abnormal uterine bleeding (suspicious for a serious condition), including bleeding 4 weeks post-septic abortion or puerperal sepsis; 10. Severely heavy or painful menstrual bleeding; 11. Suspected or known cervical, uterine or ovarian cancer, or unresolved clinically significant abnormal Pap smear requiring evaluation or treatment; 12. Any history of gestational trophoblastic disease with or without detectable elevated ß-human chorionic gonadotropin (ß-hCG) levels, or related malignant disease; 13. Any congenital or acquired uterine anomaly that may complicate study drug placement, such as: • Submucosal uterine leiomyoma • Asherman's syndromes • Pedunculated polyps

	• Bicornuate uterus • Didelphus or uterine septa 14. Any distortions of the uterine cavity (e.g. fibroids), that, in the opinion of the investigator, are likely to cause issues during insertion, retention or removal of the IUD; 15. Known anatomical abnormalities of the cervix such as severe cervical stenosis, prior trachelectomy or extensive conization that, in the opinion of the investigator would prevent cervical dilation and study drug placement; 16. Untreated or unresolved acute cervicitis or vaginitis; 17. Known or suspected human immunodeficiency virus (HIV) infection or clinical AIDS; 18. Subjects who have an established immunodeficiency; 19. Known intolerance or allergy to any components of VeraCept or ParaGard including intolerance or allergy to nickel, titanium, or copper, and including Wilson's Disease; 20. Currently participating or planning future participation in a research study of an investigational drug or device during the course of this investigational study. Subject must have waited at least 30 days from exiting their last study prior to informed consent in this study; 21. Subject has been enrolled in a previous VeraCept or LevoCept study; 22. Known or suspected alcohol or drug abuse within 12 months prior to the screening visit; 23. Any general health, mental health or behavioral condition that, in the opinion of the investigator, could represent an increased risk for the subject or would render the subject less likely to provide the needed study information; 24. Study staff or a member of the immediate family of study staff. 25. Concurrent use of corticosteroids 26. Subject is ≤4 weeks post-pregnancy (postpartum, spontaneous or induced abortion) Note: VeraCept can be inserted on any day of the menstrual cycle using the first three criteria for the Centers for Disease Control and Prevention (CDC) U.S. Selected Practice Recommendations for Contraceptive Use, 2016[10] guidance to avoid an undetected pregnancy (see the revised Box 2 below and a copy is located in the study reference manual provided to the site). If a subject has a previously inserted IUD and has pain from that IUD upon removal, then the insertion of VeraCept should not occur until the pain has resolved.

	Post Pregnancy Guidelines Subjects who were recently pregnant must have a urine pregnancy test performed no sooner than 4 weeks post-pregnancy. If a subject has not had 2 normal menses since the end of a pregnancy, the study IUD may be placed if her hCG is negative and she has been on a reliable method of contraception (e.g. pills, patch, ring) that was started within 2 weeks post-pregnancy or has been on this reliable method for 4 weeks. If the urine hCG is still positive, investigators can obtain two quantitative hCG tests that must demonstrate declining hCG values at least 1 day apart. **BOX 2. How to be reasonably certain that a woman is not pregnant**[10] A health care provider can be reasonably certain that a woman is not pregnant if she has no symptoms or signs of pregnancy and meets any one of the following criteria: • is ≤7 days after the start of normal menses • has not had sexual intercourse since the start of last normal menses • has been correctly and consistently using a reliable method of contraception* * If condoms are being used, a double barrier method must be used (e.g. condoms + spermicide).
Investigational Products, Dose, and Mode of Administration	VeraCept IUD (Test) ParaGard IUD (Reference)
Duration of treatment	The total duration of each subject's participation in this study will be approximately 57 days for the ParaGard subjects and up to 5 years for the VeraCept subjects.
Endpoints	The primary endpoint is: • Mean total serum copper concentration, Cmax, and AUC0-56 days for observed copper for each treatment The secondary endpoints are: • Mean total serum copper concentration, 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)
Criteria for Evaluation	***Pharmacokinetics*** Both baseline-corrected and observed total serum copper concentrations will be used for calculation of relevant serum PK parameters (e.g., Cmax, Cmean, AUC0-56 days) using standard non-compartmental methods and actual sampling times utilizing a PK data analysis program (e.g., Phoenix WinNonlin® or equivalent). Baseline correction will utilize the mean value of the three baseline copper concentrations. A linear up/log down method using the trapezoidal rule will be used to estimate the area under the curve. If a negative serum concentration value results after baseline correction, the value will be set to zero for the calculation of baseline-corrected PK parameters. All relevant parameters will be summarized using descriptive statistics. ***Statistical Analyses*** For the primary analysis, an 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. As such, a point estimate of the difference between treatments and 90% CIs of the difference will be provided. For the secondary analysis, an ANCOVA model with fixed effects for treatment and natural ln transformed Day 1 pre-insertion concentration as a continuous effect will be used to analyze the natural-log transformed corrected PK parameters Cmax, Cmean, and AUC0-56. 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. In addition, a shift table will also be provided for each of the PK days post Day 1 relative to the normal range. Following Day 57 (Extension Phase), serum copper concentrations will only be collected for the VeraCept treatment group. These data will be summarized in a Listing and additional statistical analysis or data presentations may be performed as appropriate.
Sample Size Determination	The assumption is that there is no additional systemic exposure of copper when using VeraCept vs ParaGard IUD. For the analysis using mean copper concentrations and Cmax, no formal hypothesis testing is being done. As such, a precision approach will be taken with boundaries chosen to reflect typical BE boundaries in the ln scale (plus or minus 22%). Assuming a normal range of 49 to 184 µg/dL, an estimate of the normal (mean) value could be close to 110-120. A comparable boundary would be

	plus or minus 22. This estimated mean with the added half-width still falls well within the normal range. For the analysis using AUC0-56 days, no formal hypothesis testing is being done. As such, a precision approach will be taken with boundaries chosen to reflect typical BE boundaries in the ln scale (plus or minus 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 half-width of at most 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.

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LIST OF IN-TEXT TABLES, FIGURES, APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
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
CFR	Code of Federal Regulations
CI	Confidence interval
Cmax	Maximum observed serum concentration
Cmean	Mean copper concentration of samples collected after Day 1 (Days 2-56)
CRU	Clinical research unit
IUD	Intrauterine Device
CV%	Coefficient of variation
eCRF	Electronic case report form
FDA	Food and Drug Administration
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional review board
PE	Physical examination
PK	Pharmacokinetic
SD	Standard deviation
SOP	Standard operating procedure
US	United States
oz	Ounce
c	Cup

1. INTRODUCTION

1.1. Background

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 (175mm^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 primary mechanism of action of the Cu-IUD is the prevention of fertilization through a cytotoxic inflammatory reaction that is spermicidal [8]. The copper concentration in cervical mucus also leads to an inhibition of sperm motility [9]. The primary mechanism in which the Cu-IUD provides contraception lies within the significant changes within the endometrial cavity, sperm quality and migration of the copper ions [10]. There is also evidence suggesting that the Cu-IUD impairs implantation [9, 11]. Copper IUDs have a first-year pregnancy-prevention success rate ranging from 97.8 to 99.9%. ParaGard, the single copper IUD approved for use in the US, can be used for up to 10 years.

The mechanism of action of a typical copper IUD is essentially a predictable electrochemical process of corrosion, driven by the IUD's immersion in the uterine fluid. Over time, the copper elements (wires, beads, tubes, etc.) corrode and release ions. Typically, the release rate is governed by the surface area and volume of copper, the chemistry (especially pH) of the uterine fluid, and the specific composition and surface properties of the copper elements.

The release rate of the copper from a copper IUD is highest during the first month after IUD placement but does not result in significant changes to serum copper levels [12].

1.2. Study Rationale

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

In order to maximize the ability to detect a difference in copper exposure following insertion of VeraCept and ParaGard, this study has been designed to sample total serum copper concentrations for the first 60 days post-insertion. Copper release rates from copper IUDs have been shown to decrease over time with the predominant decrease in release rate occurring in the first 60 days [1]. The initial release rate of copper (the burst release) appears to be correlated with the exposed surface area of copper in the device. However, as the release rates decrease over time, the release rate of copper plateaus and appears to be less dependent on the exposed surface area of the device (Figure 1-1).

Ion release testing (CTM-20141110-1) comparing VeraCept with Optima TCu380S, a commercial copper IUD with twice the exposed copper surface area, demonstrated that insertion of a copper IUD results in an initial burst of copper release followed by a steady decline in copper release rate which stabilizes by approximately 21 days of immersion (Figure 1-2). The highest average daily release rate was observed on day 1 at 1,600 ppb/day (~45 µg/day). From 21 to 60 days, the copper release rate remained relatively low and continued to decrease slightly from 278 ppb/day (~7.8 µg/day) on day 21 to 149 ppb/day (~4.2 µg/day) on day 60.

According to Chantler et al. (1977) [1], the highest copper release rate for an IUD with a similar surface area to that of the marketed ParaGard IUD is approximately 3.2 µmol/day (~200 µg/day) while the corresponding value for VeraCept is approximately 1.2 µmol/day (~75 µg/day). By 60 days, the release rate for IUDs with exposed copper surface areas similar to that of ParaGard and VeraCept decreased to below 0.5 µmol/day or approximately 30 µg/day. Long-term studies of other copper IUDs have reported similar and even lower copper release rates [2, 3].

Average daily dietary intake of copper has been reported to be approximately 1.0 to 1.6 mg/day [4-6]. Based on the data described above, by 60 days following insertion, the copper released from these IUDs would represent less than 3% of daily dietary intake of copper. Given the small amount of copper released by the IUDs relative to the total daily intake of copper, it would be difficult to attribute total serum copper concentrations to the IUD beyond this initial release period. Therefore, in order to maximize the potential to capture a difference in copper exposure following insertion of the IUD, the sampling schedule will focus on the first 60 days post-insertion (i.e. 48 hours post-insertion through Day 57).

Figure 1-1. Release Rate of Copper from Different Sizes of Copper IUDs at Five Intervals (Modified from Chantler et al, 1977)[1]

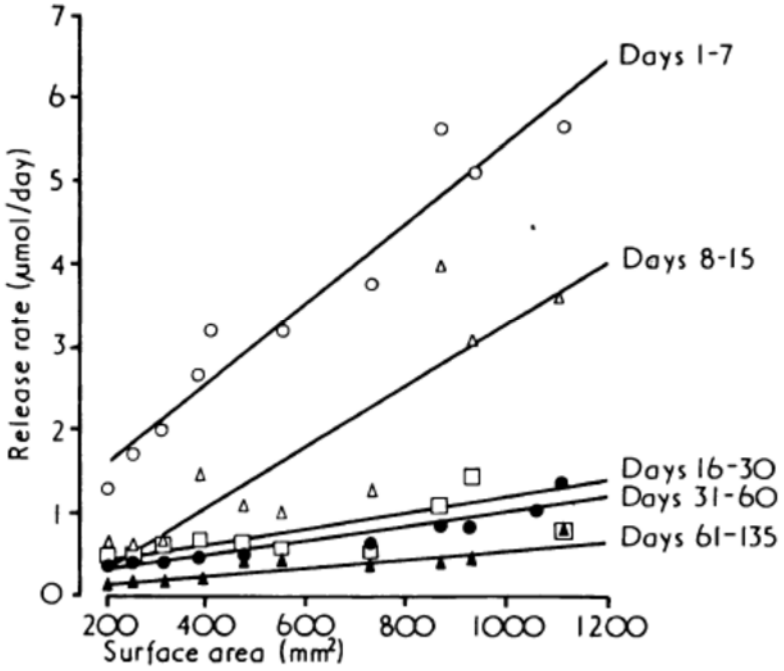
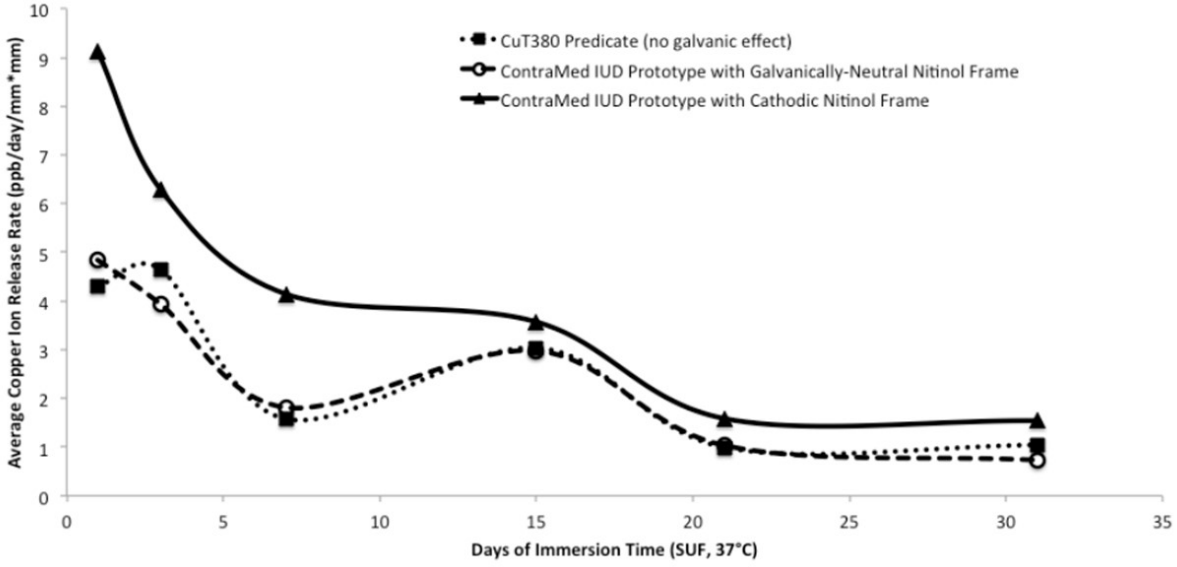


Figure 1-2. Comparison of *In Vitro* Copper Elution Rates between a Commercial Plastic-Cu IUD (CuT380) and Nitinol-Cu Sebela Devices with Different Galvanic Characteristics (from CTM-20141110-1)



2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is:

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

2.2. Secondary Objectives

The secondary objectives of this 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) [7].
- To assess the long-term stability of copper levels following insertion of the VeraCept IUD

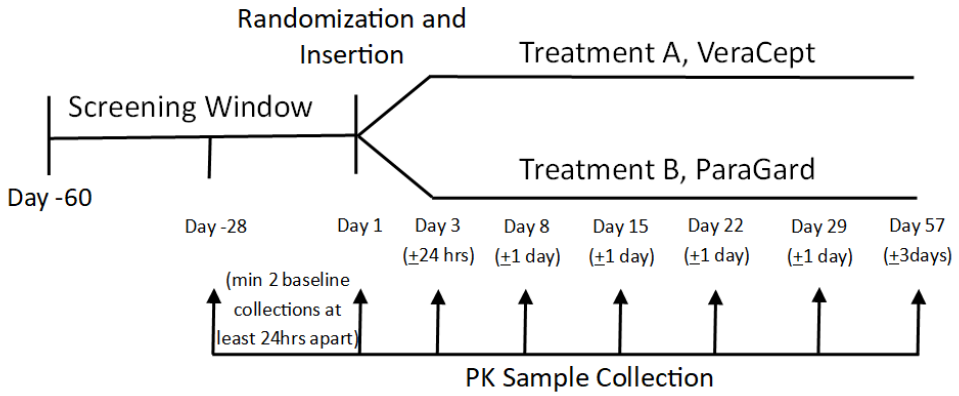
3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This parallel, open-label study is designed to evaluate the comparative bioavailability of systemic copper exposure after insertion of VeraCept intrauterine contraceptive (IUD) vs 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)

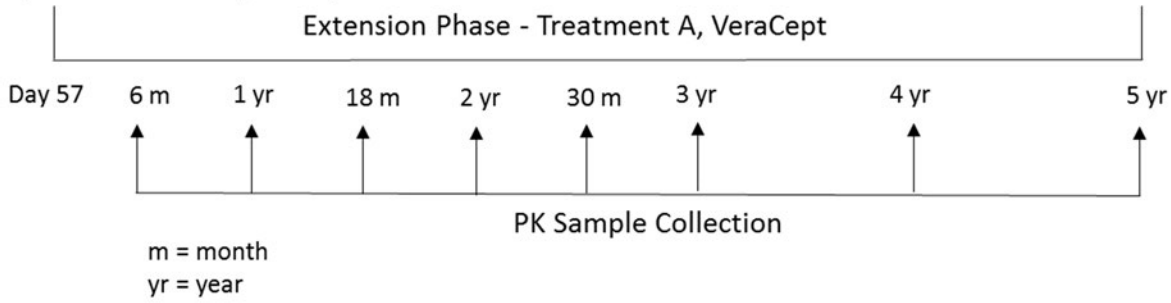
Figure 3-1. Study Design Schemata – Treatment Comparison Phase



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 3-2. Study Design Schemata – Extension Phase



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 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 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 procedures specified in Section 6.1.7 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. A schedule of the study procedures and assessments to be conducted for each subject is provided in the Time and Events Table (Appendix 1).

3.2. Primary and Secondary Endpoints

3.2.1. Primary Endpoint

The primary endpoint is:

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

3.2.2. Secondary Endpoints

The secondary endpoints are:

- Mean total serum copper concentration, 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. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

A subject will be eligible for inclusion in this study if they *meet all of the following criteria:*

1. Post-menarcheal, pre-menopausal females up to 45 years of age at the time of informed consent/assent and in good general health;
2. History of regular menstrual cycles defined as occurring every 21-35 days when not using hormones or prior to recent pregnancy or spontaneous or induced abortion;
3. Sexually active with a male partner who has not had a vasectomy;
4. Reasonably expect to have coitus at least once monthly during the study period;
5. In a mutually monogamous relationship of at least 3 months duration;
6. Seeking to avoid pregnancy for the duration of the study;
7. Willing to use the study drug as the sole form of contraception;
8. Willing to accept a risk of pregnancy;
9. Subjects must be in compliance with cervical cancer screening guidelines per the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines without evidence of disease. Subjects who are age 21-24 y/o, at time of informed consent, must have a normal papanicolaou test (Pap), atypical squamous cells of undetermined significance (ASC-US), or low-grade squamous intraepithelial lesion (LSIL). Subjects who are 25 or older at the time of informed consent with ASC-US results, must also have a negative high risk human papilloma virus (HPV) test result within the appropriate screen timeframe per American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines, and prior to the study IUD insertion. Alternatively, the subject must have had a colposcopy performed within the appropriate screen timeframe, and prior to the study IUD insertion that showed no evidence of dysplasia requiring treatment per ASCCP guidelines, or treatment was performed and follow-up at least 6 months after the treatment showed no evidence of disease by clinical evaluation;
10. Able and willing to comply with all study tests, procedures, assessment tools and follow-up;
11. Able and willing to provide and document informed consent and Authorization for Release of Protected Health Information (PHI). Unemancipated subjects under 18 years old must provide assent and have written parental consent documented on the consent form consistent with local legal requirements;
12. Plan to reside within a reasonable driving distance of a research site for the duration of the study.
13. Subject agrees not to self-remove VeraCept.

4.2. Exclusion Criteria

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

1. Known or suspected pregnancy; or at risk for pregnancy from unprotected intercourse earlier in current cycle;
2. A previously inserted intrauterine device (IUD) that has not been removed by the time the study IUD is placed;
3. History of previous IUD complications, such as perforation, expulsion, or pregnancy with IUD in place;
4. Pain with current IUD;
5. Injection of hormonal contraceptive (e.g., Depo-Provera) within the last 10 months and has not had 2 normal menstrual cycles since the last injection;
6. Use of ParaGard IUD within the past 3 months
7. Planned use of any non-contraceptive estrogen, progesterone or testosterone any time during the 60 months of study participation;
8. Exclusively breastfeeding before return of menses; lactating women will be excluded unless they have had 2 normal menstrual periods prior to enrollment;
9. Unexplained abnormal uterine bleeding (suspicious for a serious condition), including bleeding 4 weeks post-septic abortion or puerperal sepsis;
10. Severely heavy or painful menstrual bleeding;
11. Suspected or known cervical, uterine or ovarian cancer, or unresolved clinically significant abnormal Pap smear requiring evaluation or treatment;
12. Any history of gestational trophoblastic disease with or without detectable elevated ß-human chorionic gonadotropin (ß-hCG) levels, or related malignant disease;
13. Any congenital or acquired uterine anomaly that may complicate study drug placement, such as:
    - Submucosal uterine leiomyoma
    - Asherman's syndromes
    - Pedunculated polyps
    - Bicornuate uterus
    - Didelphus or uterine septa
14. Any distortions of the uterine cavity (e.g. fibroids), that, in the opinion of the investigator, are likely to cause issues during insertion, retention or removal of the IUD;
15. Known anatomical abnormalities of the cervix such as severe cervical stenosis, prior trachelectomy or extensive conization that, in the opinion of the investigator would prevent cervical dilation and study drug placement;
16. Untreated or unresolved acute cervicitis or vaginitis;
17. Known or suspected human immunodeficiency virus (HIV) infection or clinical AIDS;
18. Subjects who have an established immunodeficiency;
19. Known intolerance or allergy to any components of VeraCept or ParaGard including intolerance or allergy to nickel, titanium, or copper, and including Wilson's Disease;

20. Currently participating or planning future participation in a research study of an investigational drug or device during the course of this investigational study. Subject must have waited at least 30 days from exiting their last study prior to informed consent in this study;
21. Subject has been enrolled in a previous VeraCept or LevoCept study;
22. Known or suspected alcohol or drug abuse within 12 months prior to the screening visit;
23. Any general health, mental health or behavioral condition that, in the opinion of the investigator, could represent an increased risk for the subject or would render the subject less likely to provide the needed study information;
24. Study staff or a member of the immediate family of study staff.
25. Concurrent use of corticosteroids
26. Subject is ≤4 weeks post-pregnancy (postpartum, spontaneous or induced abortion)

Note: VeraCept can be inserted on any day of the menstrual cycle using the first three criteria for the Centers for Disease Control and Prevention (CDC) U.S. Selected Practice Recommendations for Contraceptive Use, 2016[10] guidance to avoid an undetected pregnancy (see the revised Box 2 below and a copy is located in the study reference manual provided to the site). If a subject has a previously inserted IUD and has pain from that IUD upon removal, then the insertion of VeraCept should not occur until the pain has resolved.

Post Pregnancy Guidelines

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

BOX 2. **How to be reasonably certain that a woman is not pregnant**[10]

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

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

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

4.3. Screen and Baseline Failures

Data for screen and baseline failures will be collected in source documentation at the site.

4.4. Removal of Subjects from Therapy/Premature Discontinuation

Subjects will be encouraged to complete the study and all assessments. A subject will be discontinued from the study for the following medical or administrative reasons:

- Occurrence of a treatment-emergent AE that represents an unacceptable risk to the subject and continued participation in the investigational study is not warranted per judgment of the Investigator. The Investigator must follow the subject until the AE resolves or satisfactorily stabilizes;
- Pregnancy;
- Sponsor decision;
- Subject request; and/or
- Non-compliance with the protocol.

The Investigator may discontinue individual subjects from the study at any time. Subjects may voluntarily withdraw at any time. The reason(s) for subject not completing the study will be recorded. Where subjects are "lost to follow-up", the site should make every attempt to contact the subject (3 telephone calls and if necessary, a certified letter to the subject's mailing address) so that they can be appropriately withdrawn from the study.

For subjects that fail to attend a required visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. If a subject fails to attend 2 or more visits as scheduled, the subject may be discontinued per agreement between the Sponsor and the Principal Investigator.

If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects (and assigned to the same treatment) at the discretion of the Sponsor in consultation with the Investigator.

5. TREATMENTS

5.1. Method of Assigning Subjects to Treatment Groups

After assessment of the Day 1 procedures, the subjects who qualify for enrollment will be randomly assigned to one of the following treatments in a 1:1 fashion per the randomization scheme described in Section 11.2:

- Treatment A: VeraCept, test
- Treatment B: ParaGard, reference

5.2. Treatments Administered

Insertions may only be performed by inserters that have been approved by Sebela. VeraCept can be inserted on any day of the menstrual cycle using the first three criteria for the Centers for Disease Control and Prevention (CDC) U.S. Selected Practice Recommendations for Contraceptive Use, 2016[10] guidance to avoid an undetected pregnancy (see the revised Box 2 above). If a subject has a current IUD and pain is present from removal of the IUD, insertion of VeraCept or ParaGard should not occur until the pain has resolved.

ParaGard should be used according to the ParaGard package insert which includes a description of ParaGard design and layout and instructions for use (ParaGard® T380 Prescribing Information. Trumbull, CT; Cooper Surgical, Inc; 2018).

5.3. Identity of Investigational Products(s)

5.3.1. VeraCept (Test treatment)

The VeraCept IUD is a low-dose copper-releasing IUD. The VeraCept IUD has 175mm^2 of exposed copper surface area on a shape memory nitinol frame. VeraCept is inserted using a simple two-step introducer and is provided preloaded in the introducer. The smaller diameter introducer is narrower than the ParaGard inserter.

5.3.2. ParaGard (Reference treatment)

The ParaGard IUD is a T-shaped intrauterine device with 380 ± 23 mm total exposed copper surface area. ParaGard measures 32 mm horizontally and 36 mm vertically, with a 3 mm diameter bulb at the tip of the vertical stem. A monofilament polyethylene thread is tied through the tip, resulting in two white threads, each at least 10.5 cm in length, to aid in detection and removal of the device. The T-frame is made of polyethylene with barium sulfate to aid in detecting the device under x-ray with approximately 176 mg of wire coiled along the vertical stem and a 68.7 mg collar on each side of the horizontal arm. One ParaGard weighs less than one (1) gram. No component of ParaGard or its packaging contains latex.

ParaGard is packaged together with an insertion tube and solid white rod in a Tyvek polyethylene pouch that is then sterilized. A moveable flange on the insertion tube aids in gauging the depth of insertion through the cervical canal and into the uterine cavity.

ParaGard should be used according to the ParaGard package insert which includes a description of ParaGard design and layout and instructions for use (ParaGard® T380 Prescribing Information. Trumbull, CT; Cooper Surgical, Inc; 2018).

5.3.3. Labeling

VeraCept will bear a label that meets applicable laws for an investigational drug, which includes, but is not limited to, the following information:

- Federal law statement
- Protocol number
- Lot number/ Manufacture date or expiration date
- Dosing instructions
- Storage information

5.3.4. Storage and Handling

All study products will be kept in a locked area with limited access.

Storage conditions for all study drugs are provided in the Study Reference Manual.

5.4. Selection of Doses in the Study

A single IUD (VeraCept or ParaGard) will be placed in a subject for the study. No study drug will be replaced if an expulsion or removal occurs.

5.5. Prior and Concomitant Therapy

5.5.1. Prior Therapy

All medications taken within 30 days of the screening visit will be documented in source documents and CRF (based on subject report and/or medical records).

5.5.2. Concomitant Therapy

All prescription and non-prescription medications (including herbal therapies) taken from the time of informed consent/assent until Study Exit must be documented in the source documents and CRF (brand and/or generic name, dose, dosing frequency, start and stop dates).

5.5.3. Prohibited Medications and Devices

Consumption of substances that are known to affect total serum copper levels are not permitted during this study.

The following medications and devices are prohibited:

- Known copper chelators, such as d-Penicillamine or Tetraethylenetetraamine
- Oral contraceptives containing estrogen and/or progestogens
- Treatment with corticosteroids
- Menstrual Cups
    - Subjects should be instructed to abstain from using menstrual cups to avoid accidental IUD removal during menstrual cup removal. Menstrual cup use may dramatically increase the likelihood of unintentional IUD expulsion and should not be used. If a subject cannot be discouraged from using a menstrual cup, ensure the subject is familiar with the menstrual cup instructions for use for proper insertion and removal. It is recommended that placement be low in the vagina and not in contact with the cervix. Should a menstrual cup user notice that the cup is in contact with the cervix the recommendation is to break the seal of the cup by pinching the edge of the cup first and then removing the cup.

The subject may be discontinued from the study at the discretion of the Investigator or the medical monitor if additional medications are required after the first dose of study drug through any follow-up assessments. Please contact the medical monitor or Sponsor representative if a subject requires a concomitant therapy, unless the concomitant therapy is needed immediately for subject safety.

5.5.4. Dietary Restrictions

Copper is an important nutrient and patients are not recommended to avoid foods or supplements containing copper. The Recommended Dietary Allowance (RDA) of copper for adult woman is 0.9 mg/day, the median intake of copper from food in the United States is approximately 1.0 to 1.6 mg/day, and the Tolerable Upper Intake Level (UL) for adults of 10 mg/day [13].

Patients are advised to adhere to their normal dietary patterns, but should try to avoid consuming excessive amounts of foods rich in copper, such as the foods listed in Table 5-1 below [14]. Daily or monthly serving sizes are listed for each food item, and patients should not exceed the amounts listed.

Subjects who begin to consume excessive amounts of foods rich in copper may require discontinuation from the study. The Medical Monitor should be contacted to discuss possible discontinuation of these subjects.

Table 5-1. Maximum Recommended Consumption Guidelines for Copper Rich Foods

Food Item	mg/serving	serving size	Don't exceed:
beef/calf liver	5.27	3 oz (85g)	3 oz/month
pecans	0.302	1oz (28 g)	3 oz/day
canned chili con carne	0.365	1 c (225 g)	2 cups/day
pork and beans	0.236	1/2 c	2 c/day
fried shrimp	0.181	3 oz (85g)	15 oz/day
spaghetti with meat sauce	0.258	1 c (248 g)	4 c/day
homemade lasagne	0.214	7 oz entrée (198 g)	28 oz/day
Beans (navy, pinto, red, lima, blackeye peas)	0.243	1/2 c	2 c/day
canned mushrooms	0.176	1/2 c (82g)	2.5 c/day
sweet potato	0.206	1 potato (114 g)	4/day
raisin bran cereal	0.286	1 c (56 g)	3 c/day
granola with raisins	0.216	1/2 c	2c/day
shredded wheat	0.211	2 biscuits (47g)	8 biscuits/day
oatmeal	0.194	1 c cooked, 234 g	5 c/day
chocolate milk/shake	0.226	10 oz (283 g)	40 oz/day
chocolate cake/chocolate icing	0.142	2 oz slice	14 oz/day

5.6. Treatment Compliance

The date and time of the IUD insertion, and of each PK sample collection should be recorded.

5.6.1. Study Drug Accountability

IUDs will be distributed in accordance with the procedures of this protocol. Only authorized site personnel may supply or administer the devices and only subjects enrolled in the study may receive a device, in accordance with applicable regulatory requirements.

Device accountability information will be maintained.

5.6.2. Treatment After the End of the Study

Upon completion of the procedures described within this protocol, ParaGard subjects may continue ParaGard use per standard clinical care. Subjects will not receive any additional treatment from the Sponsor. The Investigator is responsible for ensuring that consideration has been given to the post-study care for each subject.

6. STUDY PROCEDURES

6.1. Study Phases and Procedures

A Time and Events Schedule is provided in Appendix 1. Protocol deviations are not allowed with the exception of immediate safety concerns. The IRB will be informed of any safety issues that require changes to the safety monitoring or to the Informed Consent Form.

The window for screening is between Day -60 and Day 1, 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 visits prior to IUD insertion). IUD will be inserted on Day 1. The assessment period for this study is from Day 1 through Day 57.

6.1.1. Screening Window (Day -60 through Day 1)

Subjects will be screened within 60 days prior to device insertion, 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 visits prior to IUD insertion). The following procedures will be performed at Screening:

- Assess eligibility including inclusion/exclusion criteria
- Distribution of subject materials
- Informed consent and assent, if applicable, PHI and Bill of Rights forms, where applicable
- Demographics and baseline characteristics
- Medical/surgical, gynecological, and menstrual history
- Vital signs, height and weight
- General physical exam
- Pelvic exam
- Cervical cytology
- Cervical infection tests
    - 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.
    - 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.
- Pregnancy test-urine
- Prior and concurrent medication
- Subject education
- Baseline serum copper sample

    Two baseline 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 visits prior to IUD insertion)

6.1.2. Device Insertion, Day 1

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

- Assessment of Eligibility
- Vital signs and weight

- Pelvic Exam
- Transvaginal ultrasound (if clinically indicated)
- Pregnancy test (urine)
- Prior and concurrent medications
- Pre-insertion PK sample (final baseline sample)
- Adverse events and assess for any changes to health status
- IUD placement
    - If placement is unsuccessful, a second attempt may be made on the same day or within 1 week following the first attempt. If a second attempt is also unsuccessful, the subject will be discontinued early from the study.

Post IUD placement, the following evaluations will be completed:

- Pelvic exam to confirm IUD placement/string check
- Transvaginal ultrasound, if clinically indicated to confirm adequate IUD placement
- Concomitant medications
- Adverse events
- Subject education including:
    - Concomitant contraception - if there are concerns that the IUD is not properly placed, counsel the subject on the need for additional contraception

6.1.3. Day 3 (48 hours (±24 hours) post-insertion)

- Vital signs and weight
- 48-hour (±24 hours) post IUD insertion PK sample collection
- Prior and concurrent medication
- Adverse events
- Subject education including:
    - Concomitant contraception - if there are concerns that the IUD is not properly placed, counsel the subject on the need for additional contraception

6.1.4. Days 8, 15, 22, 29 (±1 day) and 57 (±3 days)

- Vital signs and weight
- PK sample collection (at approximately the same time of day as collection of the Day 3, 48-hr PK collection)
- Pelvic exam to confirm IUD placement/string check
- Transvaginal ultrasound, if clinically indicated to confirm adequate IUD placement
- Prior and concurrent medication
- Adverse events
- Subject education including:

- Concomitant contraception - if there are concerns that the IUD is not properly placed, counsel the subject on the need for additional contraception

- **ParaGard Subjects**: Day 57 (±3 days)
  - Exit Visit procedures should be completed as described in Section 6.1.6.

6.1.5. Months 6, 12, 18, 24, 30, 36, and 48 (±30 days)

- Vital signs and weight
- PK sample collection
- Pelvic exam to confirm IUD placement/string check
- Transvaginal ultrasound, if clinically indicated to confirm adequate IUD placement
- Prior and concurrent medication
- Adverse events
- Subject education including:
  - Concomitant contraception - if there are concerns that the IUD is not properly placed, counsel the subject on the need for additional contraception

6.1.6. Month 60 (±30 days) or Exit Visit

- Vital signs and weight
- Pregnancy test (urine)
- PK sample collection
- Pelvic exam to confirm IUD placement/string check
- Transvaginal ultrasound, if clinically indicated to confirm adequate IUD placement
- VeraCept removal
  - The subject's preferred method of contraception will be provided
    - If the subject elects a non-hormonal method of contraception, a 14-day supply will be provided by the site
    - If the subject elects to use hormonal contraceptive pills, a one-month supply of hormonal contraceptive pills will be provided to the subject by the site for the first 2 weeks following VeraCept removal
  - The subject will also be provided with condoms to take with her as an extra precaution if the subject fails to acquire the contraception noted above
  - Subjects should be reminded to avoid conception within 7 days after VeraCept removal
- **ParaGard Subjects**
  - Subjects may continue ParaGard use per standard clinical care or have the device removed

- If ParaGard is removed, subject's preferred method of contraception will be provided as outlined above

- Prior and concurrent medication
- Adverse events

6.1.7. Early Discontinuation Visit

All subjects who request removal of VeraCept before 5 years or ParaGard before Day 57 should follow the procedures of the Exit Visit as described in Section 6.1.6.

6.2. Study Measurements and Assessments

All study measurements and assessments to be conducted in this PK study are described below.

6.2.1. Pharmacokinetic Sample Collection and Processing

Blood samples for pharmacokinetic analysis will be collected twice during Screening at least 24 hours apart, on Day 1 prior to insertion, 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. Approximately 3-5 mL of whole blood will be collected for each blood draw. The total volume collected from each subject for all pharmacokinetic samples will be approximately 20 mL.

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

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.

6.2.2. Allergic Reaction or Hypersensitivity to Components of VeraCept

If a subject experiences allergy-related symptoms or a hypersensitivity reaction (e.g. urticarial allergic skin reaction, rash) while VeraCept is placed, she should be assessed for a possible allergy to the components of VeraCept (nickel, titanium and copper). A clinician will determine the historical relationship between symptoms and IUD use to inform a determination of causality. As needed, a nickel, titanium, and/or copper patch test will be performed and/or an assessment by a specialist for VeraCept users. If the IUD is determined to be the cause or highly suspected of causing the allergic reaction or hypersensitivity, the IUD should be removed, and the AE(s) must be followed until resolution, the condition stabilizes, 30 days post study drug removal, or the subject dies or is lost to follow up (including withdrawal of consent/assent), whichever occurs first.

7. ADVERSE EVENTS

During the study, the investigator or study site personnel will be responsible for querying and recording adverse events (AEs) and serious adverse events (SAEs), as detailed below. For the sponsor to fulfill safety assessment obligations, the investigator must report all SAEs to the

study sponsor, whether or not they result from study participation, within 24 hours of learning of the event.

7.1. Definition of a Serious Adverse Event

A serious adverse event (SAE) is any adverse event occurring within the timelines specified in the protocol that results in any of the following outcomes:

- Death;
- Life-threatening situation (subject is at immediate risk of death);
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect in the offspring of a subject who received study drug; or
- Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of serious adverse events include but are not limited to: intensive treatment in an emergency room, hospitalization for any reason, and extensive treatment at home for an adverse event. An ectopic pregnancy is considered a serious adverse event.

7.2. Definition of an Adverse Event

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

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

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

7.3. Adverse Events of Specific Interest

Adverse events of particular clinical importance, other than SAEs will be classified as adverse events of specific interest (AESIs). For this study, AESIs refer to reports of pain during insertion, pelvic infection (PID or endometritis), expulsion and uterine perforation. AESIs will be identified and assessed by the Medical Monitor during the ongoing monitoring of safety data during the trial, during DMSB meetings and for the Clinical Study Report. For each AESI, a narrative may be written and included in the Clinical Study Report.

7.4. Causality: Serious Adverse Event and Adverse Event Relationship to Study Treatment

An Investigator who is qualified in medicine must make the determination of relationship to the drug for each AE. The relationship of an AE to the drug should be assessed using the guidelines presented in Table 3. An AE for which there has been no causal relationship reported initially will require follow-up to determine causality. Of the definitions in Table 3, "possibly", "probably" and "related" to an investigational medical product are considered adverse reactions. "Unlikely" and "not related" do not qualify as a causal relationship.

Table 2: Adverse Event Relationship to Drug

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

7.4.1. Clarification of Adverse Events Related to Study Procedures

Any untoward event that occurs from the time of informed consent/assent, including the study drug placement procedure until completion of placement, or from the beginning of the removal procedure until the completion of removal, will be reported as an AE. The AE should be recorded on the AE eCRF with a causality assessment of "related to study drug placement procedure." If the AE also meets the criteria for an SAE, an SAE report should be completed and submitted to the sponsor.

7.5. Serious Adverse Event and Adverse Event Severity

The investigator will assess the severity of the AE using the following general guidelines:

Mild: An AE that is usually transient, requiring no special treatment, and does not interfere with the subject's daily activities.

Moderate: An AE that introduces a low level of inconvenience or concern to the subject and may interfere with daily activities but is usually ameliorated by simple therapeutic measures.

Severe: An AE that interrupts a subject's usually daily activity and typically requires systemic drug therapy or other treatment (a severe AE may not necessarily qualify as an SAE).

Life-threatening: An AE that put the subject at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.

Fatal: An AE that was the cause of the subject's death.

7.6. Adverse Event Outcome

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

Resolved: The subject recovered from the SAE or AE.

Resolved with sequelae: a condition whereby the consequences of a disease or injury include lingering effects.

Not Recovered/Not Resolved: At the time of the last assessment, the event is ongoing, with an undetermined outcome. Note: Ongoing SAEs and AEs are not considered resolved as a result of death and no SAE or AE stop date should be recorded for an AE that is ongoing at the time of death.

Fatal: Adverse Event directly caused death. The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a subject dies during participation in the study or during a recognized follow-up period, the sponsor should be provided with a copy of any post-mortem findings, including histopathology. Note: Death is an outcome of an adverse event and not an adverse event in itself. All reports of subject death should include an adverse event term (other than "Death") for the cause of the death.

Since reporting of an SAE is required within 24 hours of discovery, Death can be reported as an initial event term and updated to the final diagnosis in a follow-up report. If an adverse event term is not provided, the investigator will be queried to obtain the cause of death. Only in the rare occurrence that no verbatim description of an adverse event can be obtained from the investigative site will "Death – Unknown Cause" be used as the event term.

The investigator should attempt to establish a diagnosis of the event based on the signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE (and SAE if serious) and not the individual signs/symptoms.

In the case of abnormal labs or diagnostic tests judged to be clinically significant by the investigator a diagnosis, if known, or clinical signs or symptoms if the diagnosis is unknown,

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

7.7. Prompt Reporting of SAEs to Sponsor

The sponsor has requirements for reporting serious adverse events to regulatory agencies for a drug under clinical investigation. The sponsor must be notified within 24 hours of discovery if the investigator determines that an adverse event meets the protocol definition of an SAE.

All SAEs occurring from the time of IUD insertion through study exit require immediate reporting to the sponsor. Investigators should not wait to receive additional information to fully document the event prior to notifying the sponsor but should provide as much relevant information as immediately available. Further details of the event can be provided as they become available. The procedures for reporting SAEs are as follows:

- Complete the “Serious Adverse Event Report” form;
- Submit the completed form to sponsor;
- For fatal or life-threatening events, also submit copies of hospital case reports, autopsy reports, and other documents when requested and applicable;
- The sponsor may request additional information from the investigator to ensure the timely completion of accurate safety reports;
- Any fatal or life-threatening events should also be reported immediately by telephone to sponsor;
- The SAE report should be completed as thoroughly as possible and signed by the investigator before transmittal to sponsor. It is very important that the Investigator provides an assessment of the causal relationship between the event and the study drug at the time of the initial report; and
- The investigator, or responsible person according to local requirements, must comply with the applicable local regulatory requirements concerning the reporting of SAEs to regulatory authorities and the IRB.

7.8. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events and Serious Adverse Events

Abnormal laboratory findings (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g., electrocardiogram, X-rays, vital signs) per se are not reported as AEs. However, abnormal findings that are deemed clinically significant (i.e., associated with signs and/or symptoms or requiring therapeutic intervention) must be recorded as AEs if they meet the definition of an adverse event (and recorded as an SAE if they meet the criteria of being serious) as described previously. Clinically significant abnormal laboratory or other abnormal findings that are detected after study drug placement or that are present at baseline and worsen following placement of IUD are included as AEs (or SAEs if serious).

The investigator should exercise his or her medical judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. A clinically significant laboratory abnormality in the absence of clinical symptoms may also jeopardize the subject and may require intervention to prevent immediate consequences (e.g., a markedly high serum potassium concentration may not be accompanied by arrhythmia, yet be of a magnitude to require potassium-binding resin administration to prevent such sequelae). Subjects should undergo repeat testing of clinically significant abnormal laboratory findings as soon as they are recognized.

7.9. Documenting Adverse Events

Any AE occurring from the time of informed consent/assent through Study Exit must be documented in the subject's study records and on the AE eCRF. SAEs that occur during the study must be documented in the subject's study record, on the AE eCRF and on the SAE report as appropriate.

The investigator's assessment of causality, severity and status of the adverse event must be documented. When a causality assessment is provided for a serious adverse event, it is important to include a rationale for the assessment so that a better understanding of the reported event can be compiled. The rationale should be accompanied by all available supporting evidence, including relevant laboratory tests, histopathology evaluations and the results of other diagnostic procedures. The investigator's rationale with supporting evidence is valuable when sponsor performs a cumulative analysis of similar events.

7.10. Follow-up of Adverse Events and Serious Adverse Events

All AEs and SAEs must be followed until resolution, the condition stabilizes, 30 days post study drug removal, or the subject dies or is lost to follow-up (including withdrawal of consent/assent), whichever occurs first. The investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE/SAE. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals. Follow-up information should be submitted to the sponsor in a timely many as the information is obtained.

7.11. Clarification in Reporting of Deaths

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

7.12. Post-Study Treatment Reporting Requirements

For all enrolled subjects, all AEs and SAEs, regardless of cause or relationship, that occur from the beginning of study drug placement through Study Exit require reporting to the sponsor. In addition, if the investigator learns of any SAE at any time after a subject has had the study drug removed, and such event seems reasonably related to study drug, the investigator should immediately notify the sponsor.

7.13. IUD or Introducer Malfunction

Should the VeraCept IUD or its introducer not perform mechanically as expected, the sponsor should be informed. Details of the malfunction will be collected, and the sponsor

will determine if the IUD and/or introducer should be returned to the study sponsor for assessment.

Should ParaGard IUD or its introducer not perform mechanically as expected, the sponsor should be informed. Details of the malfunction will be collected.

8. PROTOCOL VIOLATIONS AND DEVIATIONS

Except in the event of a medical emergency or where it is necessary to protect the safety, rights or welfare of the study subject, any changes to the protocol will require written approval of Sebela or designee. Violations or deviations from the Clinical Investigational Plan to protect the health and safety of the subject will be reported to the IRB and as required by local regulations. All protocol violations or deviations will be recorded, tracked and reviewed periodically by Sebela and its designee, according to the process established prior to first patient enrolled. A protocol violation or deviation may be requested in advance of implementation and will be reviewed for approval by Sebela or its designee, or a violation/deviation may be identified after the fact, by the investigator, Sebela, or the monitoring staff. Investigators should ensure all scheduled PK samples are collected without protocol deviations. Investigators will be asked to provide an explanation for the all violations and deviations identified. Sebela, or designee, will be responsible for analyzing deviations and may implement corrective actions as necessary.

9. SUBJECT CONFIDENTIALITY

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

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

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

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

10. ON-TREATMENT PREGNANCY DETERMINATION AND FOLLOW UP

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

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

11. STATISTICAL CONSIDERATIONS

The statistical analysis will be conducted following the principles as specified in International Conference on Harmonisation (ICH) Topic E9 (CPMP/ICH/363/96).

All statistical and pharmacokinetic analyses will be described in a separate statistical analysis plan.

This study is designed to test the comparative bioavailability of copper as released from VeraCept vs ParaGard.

11.1. 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, AUC0-56 days). A secondary analysis will be conducted using baseline-corrected total serum copper parameters (Cmax, Cmean, AUC0-56 days).

For the analysis using Cmax and Cmean, no formal hypothesis testing is being done. As such, a precision approach will be taken with boundaries chosen to reflect typical BE boundaries in the ln scale (plus or minus 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 plus or minus 22. This estimated mean with the added half-width still falls well within the normal range.

For the analysis using AUC0-56 days, no formal hypothesis testing is being done. As such, a precision approach will be taken with boundaries chosen to reflect typical BE boundaries in the ln scale (plus or minus 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 half-width of at most 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

11.2. Randomization

Subjects will be randomized to a treatment group (VeraCept or ParaGard). The study will be conducted at one or two 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.

Once the screening assessments are performed, data have been reviewed by an investigator and the subject is considered to be eligible, the investigator or site designee will enroll the subject, assign the subject's enrollment number and determine the treatment group. The subject's number and treatment group will be determined by the sponsor provided randomization schedule. The site will assign the next consecutive subject number and corresponding treatment group. The randomization will occur on the day of first drug placement attempt. If a subject has failed two drug placement attempts, she will be withdrawn from study. Subjects will be blinded to the treatment they receive.

Subjects who drop out of the study may be replaced as agreed by the Principal Investigator and the Sponsor.

11.3. Analysis Populations

The PK study population will include all randomized subjects whose pre-insertion total serum copper concentrations were within the normal range (49 to 185 µg/dL) [7], had an IUD placed successfully, and completes all scheduled PK sample collections without a protocol deviation or AEs that significantly impact the planned PK analyses.

11.4. Pharmacokinetic Analyses

11.4.1. Pharmacokinetic Methods

Pharmacokinetic blood samples will be analyzed for total serum copper concentrations using validated bioanalytical methods. The mean of the 2 screening baseline values and the Day 1 pre-dose concentration will be used for baseline-correction.

Baseline-corrected serum concentrations that are less than zero will be treated as zero in the computation of mean baseline-corrected serum concentration values and derivation of individual subject computed parameters. Descriptive statistics (number of subjects, mean, standard deviation [SD], CV%, median, minimum, and maximum) will be used to summarize observed and baseline-corrected serum concentrations.

Both baseline corrected and observed post-dose copper concentrations will be used for calculation of relevant serum PK parameters (e.g., Cmax, Cmean, AUC0-56 days) using standard non-compartmental methods and actual sampling times utilizing a PK data analysis program (e.g., Phoenix WinNonlin® or equivalent). A linear trapezoidal method will be used to estimate the area under the curve. All relevant parameters will be summarized using descriptive statistics (number of subjects, mean, standard deviation [SD], CV%, median,

minimum, maximum, geometric mean, geometric CV%). Parameters that are less than or equal to zero will be treated as "missing".

PK Parameters to be calculated will include:

Cmax	Maximum observed concentration
Tmax	Time of maximum observed concentration
Cmean	Mean total serum copper concentration of samples collected after Day 1 (Days 3-57)
AUC0-56 days	The 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.

Total serum copper concentration and pharmacokinetic data will be listed and presented in graphical form and will be summarized descriptively by treatment group.

11.5. Statistical Analyses

For the primary analysis, an 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. As such, a point estimate of the difference between treatments and a 90% CIs of the difference will be provided.

For the secondary analysis, an ANCOVA model with fixed effects for treatment and natural ln transformed Day 1 pre-insertion concentration as a continuous effect will be used to analyze the natural-log transformed corrected PK parameters Cmax, Cmean, and AUC0-56. 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. In addition, a shift table will also be provided for each of the PK days post Day 1 relative to the normal range.

Following day 56 (Extension Phase), serum copper concentrations will only be collected for the VeraCept treatment group. These data will be summarized in a Listing and additional statistical analysis or data presentations may be performed as appropriate.

11.6. Safety Analyses

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) [7] will be assessed for each treatment. In addition, a shift table will also be provided for each of the PK days post Day 1 relative to the normal range.

Other safety analyses will be recorded and analyzed for the ParaGard subjects up to Day 57 and up to 5 years for the VeraCept subjects.

12. STUDY ADMINISTRATION

12.1. Data Monitoring and Quality Control

Sebela or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lies with the Principal Investigator generating the data.

Prior to study initiation, the Sponsor or designee will explain the protocol, Investigator's Brochure, and eCRFs to Investigators. Additionally, the monitor will explain all applicable regulations and will answer any questions regarding the conduct of the study.

The Sponsor may conduct audits (at its discretion) as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the ICH harmonized tripartite guideline E6(R1): Good Clinical Practice (GCP), the protocol, standard operating procedures (SOPs), and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. The clinic may also be compelled to undergo an inspection by a regulatory authority.

12.1.1. Data Collection and Tracking

For this study, all subject data will be entered into the electronic case report form (eCRF), transmitted electronically to the Sponsor and combined with data provided from other sources in a validated data system.

The full details of procedures for data handling will be documented in the Data Management Plan. Adverse events, medical history, and concurrent conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA, current version).

12.2. Study Responsibilities

The Investigator must provide the Sponsor with complete test results and all data collected by the Investigator from the study. During the study, only the Sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation.

12.2.1. Investigator Responsibility

The following administrative responsibilities are meant to guide the Investigator in the conduction of the study but may be subject to change based on industry and government SOPs or working practice documents or guidelines. Changes will be reported but will not result in protocol amendments.

The Investigator will permit study-related monitoring, audit(s), IRB review(s), and regulatory inspection(s), and will facilitate direct access to all the required source documents and associated records.

12.2.2. Data Transmittal and Sample/Record Retention

All data that are a result of the original observations and activities of the study and that are necessary for the reconstruction and evaluation of any study report will be retained in a secure archive at the study site for a period not less than 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have lapsed since the formal

discontinuation of the clinical development of the investigational product. Reserve samples of both the test article and the reference standard (5-times quantity) should be retained at the study site or an independent third party for a period of at least 5 years following the date of completion of the bioavailability study in which the sample from which the reserve sample was obtained.

The site will maintain a clinical study document binder, which will be maintained at the study site. In this binder, there will be sections for study documents including but not limited to the following: study personnel identification and signature list, subject screening records, subject roster (names omitted), protocol and amendments or administrative changes, study staff Curricula Vitae, study staff financial disclosures, IEC documentation, an approved sample ICF, drug accountability records, correspondence, site monitoring follow up letters, lab accreditations and normal values, significant correspondence. The site must keep this binder current and available for review by the Sponsor and/or regulatory authorities.

12.2.3. Audit/Inspections

Authorized representatives of Sebela, a regulatory authority, or an Independent Ethics Committee (IEC) may visit the site to perform audits or inspections, including source data verification. The purpose of a Sebela audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the study protocol, GCP guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The Investigator should contact Sebela immediately if contacted by a regulatory agency about an inspection.

12.3. Pharmacokinetic Sample Handling & Shipping

The procedure for pharmacokinetic sample collection, storage and shipping and the required supplies are provided in the study's Sample Collection Manual. Serum samples collected in the study will be shipped to the analytical lab for analysis per the procedures outlined in the Sample Collection Manual.

13. ETHICAL AND LEGAL CONSIDERATIONS

Study information from this protocol will be posted according to regulatory guidelines before enrollment of subjects begins.

The final study protocol, including the final version of the ICF, must be approved in writing by an IEC. The Investigator must submit written approval to Sebela before he or she can enroll any patient/subject into the study.

The Principal Investigator is responsible for informing the IEC of any amendment(s) to the protocol in accordance with local requirements. In addition, the IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IEC upon receipt of any amendments and annually, according to local regulations.

The Principal Investigator is also responsible for providing the IEC with reports of any reportable SAEs from any other study conducted with the investigational product. Sebela will provide this information to the Principal Investigator.

Progress reports and notifications of SAEs will be provided to the IEC according to local regulations and guidelines.

The Principal Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated ICF must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

14. REFERENCES

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Appendix 1. Time and Events Schedule

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]

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.
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.