CI02 A Pivotal Clinical Investigation to Evaluate the Safety and Efficacy of J3 Bioscience Lubricating Intravaginal Ring VR101 in Relieving Symptoms of Vaginal Dryness

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CONFIDENTIAL INFORMATION

DECLARATION BY THE INVESTIGATOR

I have read this protocol and agree that it contains all the necessary details for carrying out this investigation. I agree to personally conduct or supervise the investigation as described and will do all in my power to complete the investigation within the time designated. I verify that I am suitably qualified by my education, training and experience to conduct the investigation. Documentation of my qualifications and professional affiliations are contained in my Curriculum Vitae.

I will provide the copies of the protocol and all information relating to pre-clinical and prior clinical experience (i.e., Investigator's Brochure) to all staff involved in this investigation. I will discuss this material with them to ensure that they are fully conversant with the medical treatment in, and the conduct of the investigation, and that they will handle the data and information generated in the investigation confidentially.

I agree not to start enrolling participants until a duly appointed Institutional Review Board has issued a favorable opinion and the Sponsor has authorized the initiation of enrollment.

I will conduct the investigation in accordance with the provided protocol, the Good Clinical Practice guidelines of the FDA, and the spirit of the Declaration of Helsinki, and the moral, ethical, and scientific principles that justify medical research. The investigation will be conducted in accordance with the relevant laws and regulations relating to clinical investigations and the protection of participants in the country (ies) in which the investigation will be performed. All participants will be comprehensively informed about the nature of the investigation and of its investigational nature and that they may withdraw from the investigation at any time. They will give their written consent to participate before entry into the investigation. I will only use the Informed Consent Forms approved by the Institutional Review Board and the Sponsor.

I have read the Investigator's Brochure, including the potential risks of the J3 BIO investigational Vaginal Lubrication Ring VR101 and I agree to report all adverse events that may occur during the investigation.

Where applicable, the information reported in the Case Report Forms (CRFs) will be transcribed from my records, reports, and manuscripts. Either I, or an appointed person, will attest to the authenticity and completeness of the data and accuracy of the transcriptions by signing and dating the CRFs. I agree to the audit and monitoring procedures described in the protocol and contract, which involve verification of investigation records against original records and confirmation that the study is conducted in accordance with this protocol. I will make available additional background data from my records at the request of government regulatory agencies.

I understand that I am obliged to provide to the Sponsor, for the Sponsor's unrestricted use, the complete results and all data generated during the investigation, and that all information concerning VR101 and the Sponsor's activities, such as patents, formulae, manufacturing procedures, and basic unpublished scientific data and information supplied by the Sponsor,

including the investigation protocol and all investigation results, are strictly confidential and the exclusive property of the Sponsor.
I will undertake only to use this information to conduct the investigation and not to use it for any other purpose without the written agreement of the Sponsor. I will not make any changes to the protocol or propose changes to the protocol or any Sponsor-approved documents to the IRB or FDA without the written approval of the Sponsor.

I will supply the Sponsor with the investigation data in such a way that the participant cannot be personally identified.

Investigator Signature: _____

Printed Name: _____

Date: _____

List of Abbreviations and Definitions

ADE	Adverse Device Event (Effect)
AE	Adverse Event
API	Active Pharmaceutical Ingredient
CFR	Code of Federal Regulations
CHPC	Center for High Performance Computing
CIP	Clinical Investigation Plan
CI01	Clinical Investigation 01
CI02	Clinical Investigation 02
CHA	Clinical Hazard Assessment
CRA	Clinical Research Associate
CRF	Case Report Form
EC	Ethics Committee
FDA	Food and Drug Administration of United States
GCP	Good Clinical Practice
HEPA	High-Efficiency Particulate Air
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	International Organization for Standardization
IVR	Intravaginal Ring
NCR	No Carbon Required
NSR	Non-Significant Risk
OHRP	Office of Human Research Protection
PI	Principal Investigator
QSR	Quality System Regulation
SADE	Serious Adverse Device Event (Effect)
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
Sub-I	Sub-Investigator
USAE	Unanticipated Serious Adverse Event
VHI	Vaginal Health Index

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5. Post-Removal Survey (Visits 2-3, 5-9)
6. End of Use Survey (Visits 3, 6 and 8 or 9)
7. Phone Call Survey (Day 14, 21, 63 and 70)
8. Phone Call Survey (Day 35 and 147 or 175)
9. Vaginal Health Index Worksheet (all visits)
10. Adverse Event Form (used as needed)
11. Daily Diary Templates

Documents referenced in this Plan/Protocol, but not attached:

- Clinical Investigation CI01 Final Report: VR101: A Pilot Study to Evaluate the Preliminary Feasibility and Safety of a Lubricating Intravaginal Ring to Relieve the Symptoms of Vaginal Dryness
- IB02: Investigator's Brochure for CI02
- FDA Nonsignificant Risk (NSR) Device Determination Letter for VR101 (Q141385)
- Regulatory Comparison of the Predicate Device, Replens® Vaginal Moisturizer in Pre-Filled Applicators, with VR101

NOTE: The CI01 Final Report and FDA NSR Device Determination Letter are Attachments to IB02.

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1 SYNOPSIS

This investigation is designed to demonstrate the safety and efficacy of the VR101 lubricating intravaginal ring (IVR) in treating the symptoms of vaginal dryness. In the proposed investigation, participants will use VR101 devices and sham control rings in a crossover study design. Participants will also use VR101 for a total of 13 consecutive weeks to evaluate the long-term safety of the new device. The study began in the second quarter of 2017 and is anticipated to be completed in the fourth quarter of 2017.

NOTE: This revision was made effective during execution of the study to support an amendment. The purpose of this amendment is to ensure sufficient enrollment to complete the long-term safety evaluation. Please see Revision 07 for the protocol revision effective at the beginning of the study.

1.1 Sample Size

Participants will be enrolled to ensure at least 60 participants complete the investigation with a minimum of at least 20 or at least 1/3 of participants enrolled at each of a minimum of two (2) sites. (Should the number of sites be increased to increase enrollment rate, minimum number of patients per site will be adjusted accordingly.) A minimum of 30 participants will complete the long-term safety evaluation (13 consecutive weeks of VR101 use).

Based on previous experience gained during the completed pilot investigation (CI01 Study Report) where no drop-outs were observed, the drop-out rate for this investigation was statistically estimated to be no greater than 14.6%. See Section 8.4 for a detailed estimation of the drop-out rate during the long-term safety study.

As necessary to meet the total participant enrollment objective, additional qualified participants may be enrolled.

1.2 VR101 Investigational Devices

VR101 devices and sham controls manufactured by an ISO 13485-certified and/or FDA Quality System Regulation (QSR)-compliant supplier will be used in the investigation.

1.3 Summary of Endpoints (see Section 5.1.1 for details)

1.3.1 Primary Endpoints

- Device effectiveness will be assessed by determining baseline-adjusted changes in Vaginal Health Index (VHI) scores and comparing the changes in VHI scores recorded for VR101 use (ΔVHI_{VR101}) with the changes in VHI scores recorded for use of sham control rings (ΔVHI_{sham}) following 28 days of continuous ring use.

- Device safety will be assessed by determining the proportion of Serious Adverse Device Effects (SADEs) resulting from VR101 use over the course of the study.

1.3.2 Validation of Labeling Claims

The following labeling claims will be evaluated:

- Each VR101 relieves the symptoms of vaginal dryness for up to 7 days
- VR101 is easy to use by following the provided instructions
- VR101 is comfortable during use

1.4 Brief Summary of Clinical Procedures (see Section 5.4 for details)

After each participant has read and signed the Consent Form(s), she randomly will be assigned to one of two groups:

- The first group (designated "V1S2") will use VR101 for 4 weeks, followed by a three-week "washout" period, and then use the sham control for 4 weeks.

- The second group (designated "S1V2") will use the sham control for 4 weeks, followed by a three-week "washout" period, and then use VR101 for 4 weeks.

  NOTE: VR101 devices and sham controls will be replaced by participants every 7 days over the initial 28-day period (each of the 4 rings will remain inserted for 7 days before being replaced by a fresh ring), for a total of 4 successive uses of the devices or of 4 successive uses of the sham controls over the initial 28 days of the study.

- Participants in the S1V2 group will continue to use an additional 9 VR101 devices successively, each for one week resulting in the use, by each S1V2 participant, of 13 VR101 devices for a total duration of 13 weeks.

- Participants in the V1S2 group will, after the 3-week washout period, use 4 shams successively, each for one week.

- All participants will then be automatically selected to use VR101 for a total of 13 consecutive weeks in the safety portion of the investigation.

  - V1S2 participants will be provided with additional VR101 devices to allow for 13 consecutive weeks of use.
  - Upon receiving written consent to participate in the safety portion of the investigation, S1V2 participants will be provided with additional VR101 devices to allow for 13 consecutive weeks of use.

Note that the 4 weeks of continuous use of VR101 use by S1V2 participants in the second portion of the crossover study will constitute the first 4 weeks of the 13 weeks of consecutive use of the device for the safety portion of the investigation. In contrast, V1S2 participants will be provided with enough VR101 devices to complete the 13-week safety portion of the investigation, and will complete the investigation approximately 4 weeks after S1V2 participants.

2 BACKGROUND

2.1 Purpose

The purpose of this Clinical Investigation Plan (CIP) is to document and detail the activities required to conduct a clinical investigation of VR101 entitled "**A Pivotal Clinical Investigation to Evaluate the Safety and Efficacy of J3 Bioscience Lubricating Intravaginal Ring VR101 in Relieving Symptoms of Vaginal Dryness**," internally designated "CI02." CI02 is a planned pivotal investigation designed to evaluate the safety and efficacy of VR101 and establish its substantial equivalence to the predicate de-vice, building on the results obtained in CI01, "VR101: A Pilot Study to Evaluate the Preliminary Feasibility and Safety of a Lubricating Intravaginal Ring to Relieve the Symptoms of Vaginal Dryness." The data from CI02 will be used to support a premarket 510(k) notification to the FDA to enable regulatory clearance of the device in the United States (US). The investigation is designed to comply with the requirements of ISO 14155, allowing the investigation to also support regulatory submissions and registrations in other countries or regions.

2.2 Scope

This procedure applies to the clinical investigation of VR101, a vaginal lubrication ring manufactured by J3 Bioscience, Inc. (J3 BIO), to establish the safety and efficacy of VR101 in relieving symptoms of vaginal dryness and its equivalence to the predicate device. Results may be applicable to other versions of J3 BIO device designs. Justification for applicability of results to other designs will be documented in the relevant technical documentation (i.e., design history file, technical file, or other files).

2.3 Summary of VR101 Bench Testing

2.3.1 Performance Tests

The following characteristics of VR101 devices have been evaluated and found to be acceptable:

- Visual appearance
- Mass
- Dimensions
- Mechanical force required to compress VR101
- Tensile strength
- *In vitro* release of glycerol
- Shelf-life and stability

- Condom compatibility

Details of the evaluations performed and results obtained can be found in the Investigator's Brochure (CI02 Investigator's Brochure IB02 Rev 02) for CI02.

2.3.2 Biocompatibility Tests

The biological and toxicological safety tests conducted on VR101 and its components consists of ISO 10993-1 and FDA-recommended studies. The ISO 10993-1 and FDA-recommended studies completed include cytotoxicity (L929 MEM elution and agar overlay), genotoxicity (Ames mutagenicity), guinea pig maximization sensitization (Magnusson-Kligman method), vaginal irritation (rabbit, mucosal), and acute systemic injection (IV and IP) tests. Results of these tests performed either on the VR101 test articles or VR101 components, as appropriate, were acceptable, suggesting VR101 and its components will not elicit an unacceptable biological or toxicological response under anticipated end-use conditions.

Additionally, cytotoxicity testing sponsored by Thermedics, Inc. (now Lubrizol Advanced Materials, Cleveland, OH) of the raw Tecophilic® HP-60D-35 polymer (Lot #E999-03235, now renamed Excipient Grade Thermoplastic Urethane Pathway® Polymer PY-PT42DE35) was performed at Toxikon Laboratories (Bedford, MA). The extracts of the polymer test article showed no evidence of reactivity in these studies. Thus, the raw polymer test article is considered non-cytotoxic under the conditions of this sensitive screening test.

On the basis of the results obtained in the ISO 10993-1 and FDA-recommended studies, J3 BIO concluded that the biological and toxicological risks associated with the use of VR101 are low and acceptable, justifying the initiation of the pilot investigation. This conclusion was validated by the results of CI01, where no reports of irritation, toxic reactions, or other biological responses to the device were reported.

To assure an acceptable biological risk with the use of VR 101 in the long-term clinical safety portion of this investigation, J3 BIO will complete additional biocompatibility studies concurrently with the execution of CI02. A detailed summary of completed and planned biocompatibility assessments can be found in IB02, Section 3.3.

2.3.3 Summary of VR101 Preclinical Testing

J3 BIO and the University of Utah (Department of Bioengineering) conducted nonclinical *in vivo* efficacy studies in a sheep model to support the development of and establish feasibility of VR101 use in providing vaginal moisturization and lubrication. The model was selected because there are similarities between human and sheep vaginal size and shape. Studies were performed to assess the release of the lubricant solution and the ability of VR101 to moisturize and lubricate the sheep vaginal tract. Vaginal fluid was collected for up to 7 days using standard techniques during insertion of either VR101 or

"placebo" (empty reservoir, non-glycerol-releasing) hydrophilic polyurethane (HPU) sham ring to assess potential effectiveness. Over the 7-day study period, sheep treated with VR101 exhibited a statistically significant increase in available vaginal fluid versus placebo-treated and baseline control subjects. Collected fluid volumes were 4.6-fold higher in VR101-treated animals compared to placebo-treated animals. These results indicate that use of the VR101 device may increase vaginal fluid volumes in humans and supported the evaluation of VR101 in subsequent clinical investigations.

2.4 Summary of VR101 Pilot Study

J3 BIO successfully completed the first-in-human pilot clinical investigation (CI01) in 21 consenting peri- and post-menopausal women to assess preliminary safety and feasibility of use of VR101 in relieving the symptoms of vaginal dryness. The study was conducted at the Department of Obstetrics and Gynecology at the University of Utah Health Sciences Center. In the study, participants were instructed to use two VR101 devices consecutively, each for 7 consecutive days, for a total of 14 continuous days of VR101 use. Participants visited the clinic a total of four times (typically following 0, 3, 7, and 14 consecutive days of device use, respectively). During each visit, a vaginal health assessment was administered by a clinician. In addition, participants completed a Daily Diary and answered several survey questions to assess their experience with use of VR101.

Overall, participants reported that they were satisfied with VR101 and confident that it was working. Average responses to survey questions assessing participants' positive satisfaction and confidence during and after VR101 use consistently ranked between "Agree a Lot" and "Agree Completely." Furthermore, encouraging results were achieved when assessing relief of vaginal dryness objectively using a modified composite Vaginal Health Index (VHI) score which equally weighted clinical assessments of vaginal elasticity, fluid volume, epithelial integrity and moisture. Across the study population, mean composite modified VHI scores increased versus baseline values collected before device insertion during Visit 1 at each subsequent visit, with statistically significant increases ($p \leq 0.05$, one-tailed, normally approximated Wilcoxon signed-rank test) observed during Visits 2 and 4 occurring 3 and 14 days, respectively, after the insertion of the first VR101.

Participating women also were asked to report the frequency of their vaginal dryness symptoms throughout the study. They initially reported experiencing dryness an average of 4 days out of the prior 7 days. Once participants started using VR101, the reported frequency of vaginal dryness symptoms decreased to an average of 1.3 days during the first 7 days of ring use, 0.4 days during the second 7 days of ring use and remained lower than baseline 7 days after discontinuing ring use (1.8 days out of 7 days after VR101 use had been discontinued) (all $p < 0.005$, one-tailed, normally approximated Wilcoxon signed-rank test). While 20 of 21 women reported experiencing dryness symptoms in the 7 days prior to entering the study, only 7 of 21 and 4 of 21 reported experiencing any symptoms of vaginal dryness during the first and second week of VR101 use, respectively.

Regarding safety, no serious safety concerns or adverse events were noted or reported by the participants or clinical study staff. Participants were asked if they experienced any unusual vaginal discomfort or discharge over the course of the investigation. There were 11 reports (out of 63 total surveys) of vaginal discomfort recorded and six reports (out of 63 total surveys) of vaginal discharge. It is important to note that for both vaginal discomfort and discharge reported, all participants but one rated discomfort and discharge with the lowest intensity score possible, "minimal/minor," and that none of the participants consistently reported unusual discomfort or discharge throughout the study. Moreover, all 21 participants that enrolled successfully completed the study, including follow-up.

In total, these results demonstrate that VR101 shows promise for safely moisturizing and lubricating the vagina and supplementing the body's natural lubrication in peri- and post-menopausal women experiencing symptoms of vaginal dryness. A complete summary of data from the pilot investigation CI01 can be found in Clinical Investigation CI01 Final Report which is included as an attachment to the Investigator's Brochure.

3 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

3.1 Summary Description of VR101

VR101 is a clear, flexible, torus-shaped device (intravaginal ring (IVR); see Figure 1, Device Image, and Figure 2, VR101 Schematic Drawing). VR101 is manufactured from hollow tubing formed from Excipient Grade Thermoplastic Urethane Pathway® Polymer PY-PT42DE35 (identical to Tecophilic® HP-60D-35 (Lubrizol Advanced Materials, Cleveland, OH) by hot-melt extrusion.

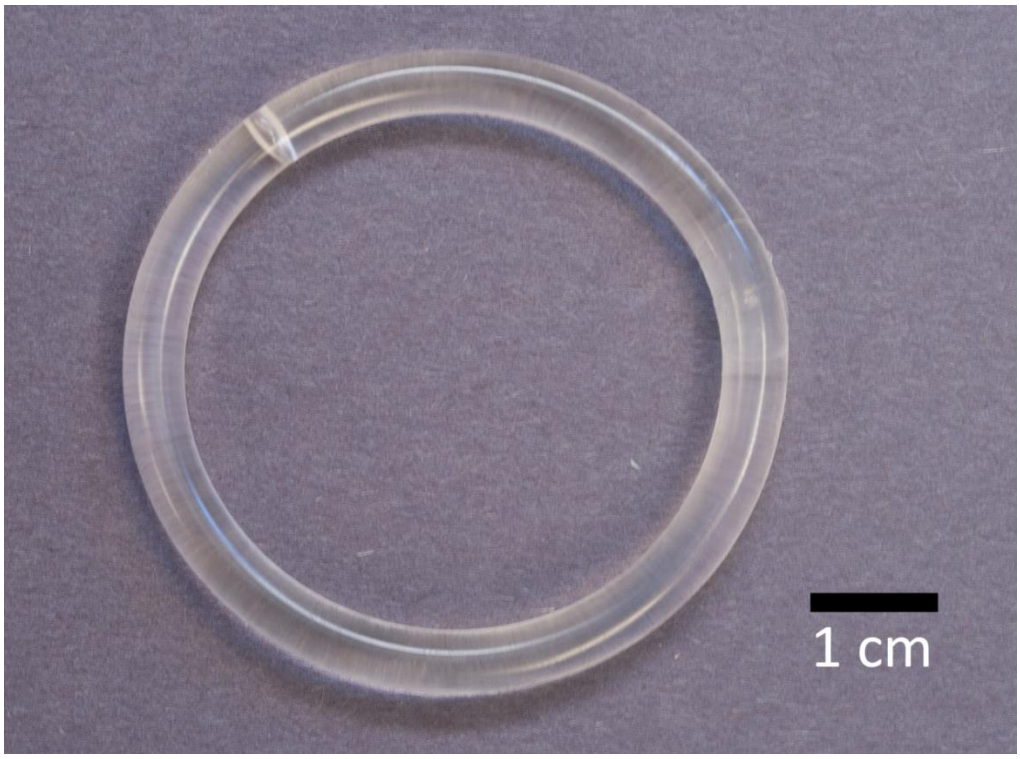

Figure 1. Top View of VR101

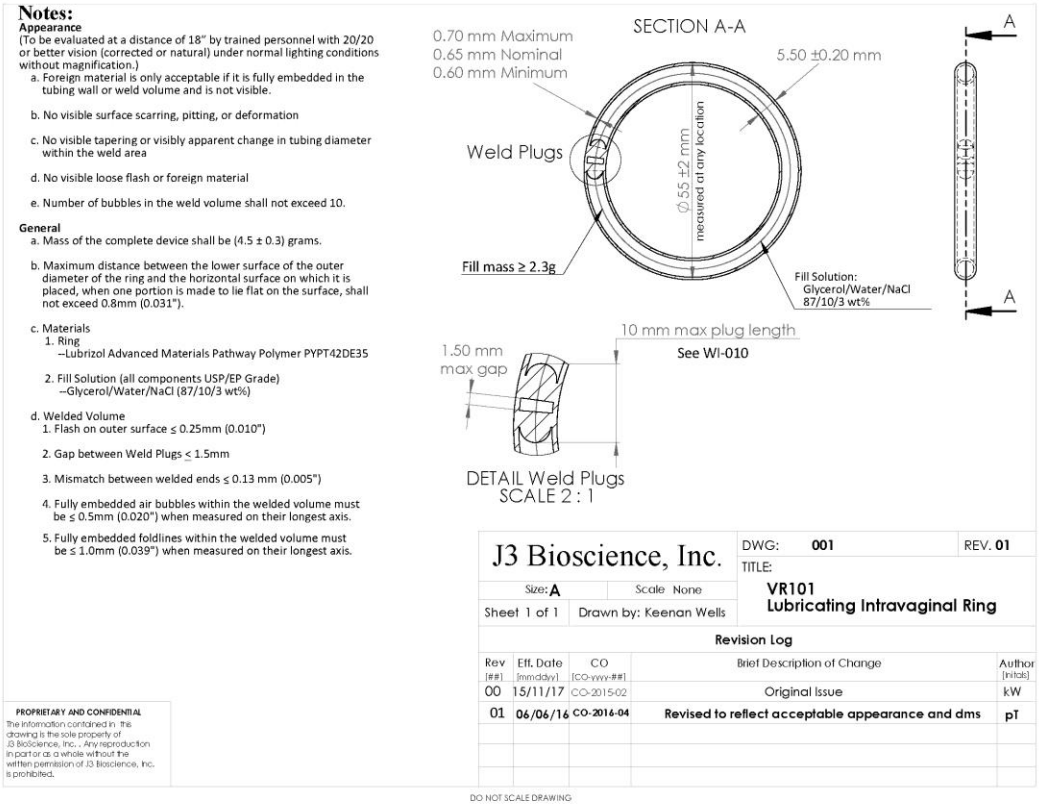

Figure 2. VR101 Manufacturing Drawing with Specifications

The VR101 manufacturing process consists of extruding tubing from Excipient Grade Thermoplastic Urethane Pathway® Polymer PY-PT42DE35 (formerly Tecophilic HP-60D-35) and cutting the extruded tubing into short segments that are the length of the eventual circumference of the finished VR101 devices. The tubing segments are filled with a solution of 87/10/3 (wt %) USP grade glycerol/USP grade water/USP grade sodium chloride solution. The ends of the tubing are subsequently thermally fused to form a continuous ring. The filled ring is placed into a mold and briefly heated in an annealing step to release stresses and form the ring into its final circular shape. The rings are packaged in foil-backed polyethylene pouches containing 0.25 mL of a glycerol/water solution.

Device dimensions are comparable to commercially available IVRs. Table 1 lists the dimensions of VR101. Table 2 identifies composition and weight of VR101. Table 3 provides the specifications for VR101 constituents. VR101 does not contain any drugs or active pharmaceutical ingredients (APIs).

Table 1. Nominal Dimensions of VR101	
Ring Characteristic	**Dimension**
Outer Diameter (ring)	55 mm
Cross-Sectional Diameter (tubing)	5.50 mm
Wall thickness (tubing)	0.60 mm (min.)

Table 2: Nominal Composition and Weight of VR101	
Device Component	Weight
Tubing Pathway® PY-PT42DE35	2.0 g
Lubricant Solution (Liquid Core)	2.5 g (total)
Glycerol, USP	2.2 g
Water, USP	0.2 g
Sodium Chloride, USP	0.1 g
Total Mass	4.5 g

Table 3. Detailed Specifications for VR101 Constituents	
Ring	
Component	*Material Description*
Tubing	Hydrophilic aliphatic polyether urethane (HPU) tubing, extruded from Lubrizol medical grade Pathway™ PY-PT42DE35
Lubricant Solution (present in the Lumen of VR 101, also referred to as "Liquid Core")	
Glycerol	Glycerol, Synthetic Chemical Abstract Services: CAS #: 56-81-5 Molecular Formula: $C_3H_8O_3$ Meets relevant standards listed in: • EP: European Pharmacopeia • USP: United States Pharmacopeia • BP: British Pharmacopeia • JP: Japanese Pharmacopoeia Certified free from Bovine and Transmissible Spongiform Encephalopathy
Water	Water, Deionized CAS # 7732-18-5 Molecular Formula: H_2O Meets relevant standards listed in: • EP: European Pharmacopeia • USP: United States Pharmacopeia • JP: Japanese Pharmacopoeia

Table 3. Detailed Specifications for VR101 Constituents	
Sodium Chloride	Sodium Chloride CAS # 7647-14-5 Molecular Formula: NaCl Meets relevant standards identified in: • EP: European Pharmacopeia • USP: United States Pharmacopeia

3.2 Principles of Operation of VR101

Upon insertion, the glycerol solution in the VR101 device begins to pass through the semipermeable polyurethane ring wall into the vagina where it provides lubrication and moisture. The release of the glycerol solution is prolonged as its transport into the vagina is modulated by the presence of the polyurethane ring wall.

3.3 Intended Purpose of VR101

VR101 is a personal lubrication device, for vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. VR101 is designed to relieve symptoms of vaginal dryness for up to 7 days.

Glycerol is a lubricating agent, generally recognized as safe (GRAS) by the FDA, with a long history of safe clinical use in vaginal applications. The intended duration of vaginal lubrication (7 consecutive days) provided by each VR101 device is based on the results of preclinical evaluations in sheep and a pilot study (CI01) conducted in humans. See Sections 2.3.3 and 2.4 above for summaries of the preclinical and pilot clinical studies, respectively.

3.4 Supplier of VR101 Devices and Sham Controls

VR101 devices and sham controls manufactured by an ISO 13485-certified and/or FDA Quality System Regulation (QSR)-compliant supplier will be used in the investigation.

3.5 VR101 Identification

The individual packages containing each investigational device or sham control will be labeled with the device name ("VR101 Lubricating Vaginal Ring") and expiration date. They also will be labeled with the statement “for investigational use only” (see Section 5.6, below).

3.6 VR101 Lot Traceability

VR101 devices are assigned a unique lot identifier by the contract manufacturer or J3 BIO. All components of and materials used in the finished devices are traceable to their suppliers and supplier lot numbers.

3.7 Training and procedures required to use VR101

No medical or surgical intervention or clinician involvement is required to use VR101 safely and effectively. VR101 is designed to be self-inserted by users of the device and remain in place for up to 7 consecutive days. After 7 days, the ring is removed by the user, discarded, and, at the user's discretion, replaced with a fresh ring.

VR101 is intended to be available as an OTC (Over-the-Counter) product that will not require healthcare professional assistance or supervision for use and/or as a prescription-only use device. In both cases, the user will not be assisted with use of the device. As such, the user must be able to insert and remove the device solely on the basis of reading the provided instructions for use (IFU) and labeling. Participants in CI01, the pilot clinical investigation, demonstrated, in all cases, an ability to insert and remove VR101 without physician assistance or consultation.

3.8 Sham controls

Sham control rings will be manufactured for the purpose of providing a control to enable evaluation of the efficacy of the release of the lubricating solution from VR101 in this investigation, when compared with the effects of the presence of the ring, alone. The sham control will be manufactured, packaged, and labeled identically to VR101, with the exception that the hollow ring lumen will not be filled with the glycerol solution described in Table 3. That is, the core of the sham control rings will contain no lubricating solution, but the packaging will still contain 0.25 mL of glycerol/water solution to aid in device insertion.

4 OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

4.1 Study Objectives

4.1.1 Primary Objectives of CI02, the Proposed Pivotal Clinical Investigation

- To demonstrate the efficacy of VR101 in treating the symptoms of vaginal dryness in women by showing that the change in VHI composite scores following 28 days of continuous VR101 use (consisting of use of 4 each VR101 devices consecutively, each for 7 consecutive days) is statistically superior to the changes in VHI composite scores following 28 days of continuous sham control use (consisting of use of 4 each sham rings consecutively, each for 7 consecutive days).
- To assess the safety of VR101 when used to treat the symptoms of vaginal dryness.

4.1.2 Validate Claims

- Claim 1: VR101 relieves the symptoms of vaginal dryness for up to 7 days.
- Claim 2: VR101 is easy to use by following the provided instructions.
- Claim 3: VR101 is comfortable during use.

4.1.3 Demonstrate Usability

Validation of Claim 2 will justify Over-the-Counter (OTC) use of VR101.

4.1.4 Conduct Exploratory Evaluations

Additional survey questions may be asked of participants to further the scientific and technical understanding of VR101, as well as user preferences.

4.2 Hypotheses of the Clinical Investigation

The clinical investigation CI02 is designed to demonstrate that the efficacy and safety of VR101 are substantially equivalent to the safety and efficacy of the predicate device, Replens® Long-lasting Vaginal Moisturizer in Pre-Filled Applicators. Substantial Equivalence will be assessed through the evaluation of the ability of clinical use of VR101 to meet safety and efficacy endpoints.

4.2.1 Primary Efficacy Hypothesis

Primary Efficacy Hypothesis: VR101 will relieve symptoms of vaginal dryness to a degree statistically superior to that of a sham control, when assessed objectively by a clinician who assigns VHI scores before and following 28 consecutive days of VR101 and sham control use (4 VR101 devices or shams used consecutively, each for 7 consecutive days).

The relief of vaginal dryness symptoms will be assessed throughout the study using composite Vaginal Health Index (VHI) scores, which are a sum of clinician-assigned scores for Vaginal Elasticity, Fluid Volume, Epithelial Integrity, Moisture and pH each weighted equally. This identical VHI composite score was used to evaluate the effectiveness of the predicate device (Replens) in clinical investigations that supported 510(k) premarket notification K101098, cleared by the FDA to allow marketing of the Replens device in the US.

ΔVHI resulting from use of VR101 or the sham control will first be determined by subtracting a participant's baseline VHI score from her day 28 VHI score, when using either the VR101 or the sham control. For example, if a participant's baseline VHI composite score is 15 and her VHI score following use of VR101 for 28 days is 22, ΔVHI_{VR101} at day 28 would be 22 – 15 = 7.

Superiority of VR101 to the sham control will be demonstrated if the *p*-value associated with a two-tailed Student's t-test evaluating the mean of the paired differences ΔVHI_{VR101} (day 28)

and ΔVHI_{sham} (day 28) is less than 0.05. If the paired differences observed are not normally distributed, an appropriate non-parametric test will be substituted for the two-tailed Student's t-test. Additionally, a two-tailed 95% confidence interval of the mean paired difference will be reported.

The same 95% confidence interval for the menopausal population (see section 8.12) will be reported.

NOTE: It is possible to demonstrate statistical superiority and for the mean value of ΔVHI_{VR101} (day 28) to be less than or equal to zero. Efficacy of VR101 will only be demonstrated if VR101 statistical superiority is demonstrated AND the mean value of ΔVHI_{VR101} (day 28) is greater than 0. That is, use of VR101 must not only be superior to that of the sham control, but must also demonstrate a positive improvement in VHI score.

4.2.2 Safety Hypothesis

Primary Safety Hypothesis: VR101, when used in accordance with provided instructions for use will not result in a rate of occurrence of Serious Adverse Device Effects (SADE) greater than 1%.

P(safety) = proportion of initiated VR101 uses without a Serious Adverse Device Effect, which is equal to: Total number of initiated VR101 uses without a participant reporting a serious adverse device effect during VR101 use divided by the total number VR101 devices used.

VR101 safety will be demonstrated if the upper bound of the two-sided exact 95% confidence interval surrounding the proportion of SADE occurrence ('P(SADE)') is 0.01 or less.

4.2.3 Hypotheses for Claims and Usability Testing

If both the primary efficacy and safety hypotheses are met, then hypotheses for Claims 1, 2, and 3 will be tested using a hierarchical testing approach in order to control for multiplicity. Claim 1 will be tested first and if the null hypothesis is rejected, then Claim 2 will be tested. If the null hypothesis for Claim 2 is rejected, then Claim 3 will be tested. Refer to Appendix B for survey questions used to assess the validity of the following claims.

Claim 1: VR101 relieves vaginal dryness symptoms for up to 7 days in a majority of participants, as assessed by users.

Vaginal dryness severity will be assessed throughout the study using participant's ranked responses to questions in a questionnaire (see Section 5.4.5 below). Severity will be scored on a 0 to 3 scale (3 being the worst possible rating). At each visit, participants will be asked to rate their vaginal dryness over the last 24 hours and the last 7 days. **Claim 1 will be validated if the**

***p*-value associated with a two-tailed Student's t-test of the mean of the paired values between the *daily* vaginal dryness severity score reported on day 7 (survey question, Visit 2) and average *weekly* vaginal dryness severity score reported over the week prior to VR101 use (survey question, Visit 1 for study group V1S2, Visit 4 for study group S1V2) is less than 0.05.** If the paired differences are observed not to be normally distributed, an appropriate non-parametric test will be substituted for the two-tailed Student's t-test. Additionally, a two-tailed 95% confidence interval of the paired dryness values will be reported.

Claim 2: VR101 is easy to use by following the provided instructions for use.

Null and Alternative Hypotheses for Claim 2:

When the first ring is removed (Day 7, Visit 2/5 depending on study group), the participant will be asked to rate her level of agreement with the statement "the ring was easy to use by following the provided instructions" on a scale of -4 to 4 (see section 5.4.6). Claim 2 will be validated if the lower bound of the two-sided 95% confidence interval of the proportion of the study population that recorded favorable responses (participants recording a Score of 1, 2, 3 or 4) is greater than or equal to 0.80. The 95% confidence interval will be calculated using the exact test.

Claim 3: VR101 is comfortable during use.
In each daily diary, the participant will be asked to rate her level of agreement with the statement "the ring was comfortable to me today" on a scale of -4 to 4 (see section 5.4.6). Claim 3 will be validated if the lower bound of the 95% confidence interval of the proportion of the study population that recorded favorable responses (participants recording a Score of 1, 2, 3 or 4) is greater than or equal to 0.80. The 95% confidence interval will be calculated using the exact test.

5 STUDY DESIGN

5.1 General Description of the Clinical Investigation

Clinical Phase: Pivotal

Sample Size: At least 60 participants (up to 69 may be enrolled to account for the anticipated drop-out rate) who consent to be enrolled and meet inclusion/exclusion criteria

Study Population: Women over the age of 35 who self-report having experienced vaginal dryness symptoms that interfere with daily activities, including but not limited to sexual activity, in the last 60 days; and whose clinician-assigned baseline VHI score is 22 or lower.

Study Type (Comparative Efficacy): Multi-center, investigator- and participant-blind, randomized crossover study.

Study Type (Long-term Safety): Multi-center, long-term safety evaluation

Study Products: VR101 devices and sham controls (see descriptions above)

Study Regimen: Participants will be randomly assigned to be treated initially by VR101 (GROUP V1S2) or a sham control (GROUP S1V2). Since inclusion in the study will be contingent upon a sufficiently low baseline VHI score, official enrollment and randomization will not occur until the participant's baseline VHI score has been measured and determined to meet the inclusion criterion (Initial VHI ≤ 22). Participants randomly assigned to GROUP V1S2 will insert a VR101 ring and leave it in place for 7 days, then remove the first ring and replace it with a fresh ring on day 7. Subsequently, 2 additional rings will be inserted and removed serially on a 7-day schedule until a total of 4 rings are used by each study participant, with the last ring removed at day 28.

Participants assigned to S1V2 will insert a sham control ring and leave it in place for 7 days, then remove the first ring and replace it with a new ring on day 7. Subsequently, 2 additional sham rings will be inserted and removed serially on a 7-day schedule until a total of 4 sham rings are used by each study participant, with the last sham ring removed at day 28.

Following completion of the first 28-day treatment course with either VR101 or sham control, participants will undergo a 21-day "washout" period during which no devices will be used, before "crossing over" to treatment with the other device.

Participants in Group S1V2 will be assigned to complete the long-term safety evaluation. Following the 4-week use of shams and a 3-week washout period, these participants will use a new VR101 device every 7 days for 13 consecutive weeks. V1S2 participants will be transitioned back to VR101 following 4 weeks of sham use, and will use VR101 for 13 additional weeks.

NOTE: VHI scores will be collected during the long-term safety evaluation, but those scores assigned after day 28 will not be used as a measure of device efficacy.

5.1.1 Study Endpoints

Used to Test Primary Efficacy Hypothesis:

1. ΔVHI_{VR101} (day 28) – ΔVHI_{sham} (day 28), the paired difference in vaginal dryness relief between VR101 and the sham control at day 28.

Used for Validation of Claim 1:

2. The paired difference between self-reported 24-hour vaginal dryness severity reported after the first 7 days of VR101 use (see Section 5.4.5, collected at Visit 2 or 5 depending on study group) and weekly-averaged vaginal dryness severity prior to ring use (also see Section 5.4.5, collected at Visit 1 or Visit 4 depending on study group).

Used for Validation of Claim 2:

3. Participant reported ease of use of VR101 (measured on a scale of -4 to 4, see Section 5.4.6).

Used for Validation of Claim 3:

4. Self-reported perception that VR101 was comfortable during use, measured on a scale of -4 to 4 (see Section 5.4.6).

Used to Test Primary Safety Hypothesis:

5. The proportion of Serious Adverse Device Effects (SADE) in relation to the total number of VR101 devices use in the study.

5.1.2 Measures to Minimize Bias

- Clinicians assigned to perform vaginal exams and assign VHI Scores will be blinded from device identity, and thus upon administering an exam will not be aware of whether a patient has inserted a VR101 or a sham ring.
- Because lubricant-filled VR101 devices and unfilled sham rings are very similar in appearance and both are packaged with the same amount of excess glycerol/water solution, it is likely that patients will not know whether they are inserting the test VR101 devices or the sham controls.
- Clinicians assigned to perform vaginal exams and collect VHI Scores will be blinded from accessing any patient data from previous visits pertaining to efficacy endpoints (see section 5.1.1). Thus, on any given visit, the clinician assigned to measure VHI will be unaware of a patient's previous VHI score.
- Participants will not have access to their previous responses, and thus in any given survey where subjective data are collected for the validation of claims, participants will be unable to reference their previous responses.
- Any women who meet inclusion/exclusion criteria and consent to be enrolled in the study will be enrolled and randomly assigned to either the V1S2 or S1V2 treatment group.
- To preserve assigned randomization identity during the crossover study, V1S2 participants will be transitioned back to VR101 following 4 weeks of sham use and will participate in the long-term safety study.

5.1.3 Test Equipment, Maintenance, and Calibration

No special test equipment is required for assessing the effects of VR101, with the exception of the assessment of vaginal pH. Vaginal pH shall be measured using Precision Labs Beer pH Strips (Cat. No. PH4662). Operators will be trained use pH strips per the manufacturer's instructions. pH shall be recorded to the nearest 0.2 pH units on the applicable Case Report Form.
No other test equipment is needed for evaluation of safety or efficacy of device use.

5.2 Investigational and Predicate Devices

5.2.1 Exposure to VR101 and the sham control

Participants will use VR101 for up to 17 weeks total and the sham control for 4 weeks as described above. Participants will use VR101 for approximately 13 total weeks, consecutively, to evaluate device safety.

5.2.2 Justification for the Choice of Replens® as a Predicate Device

The new VR101 and predicate Replens® devices have identical intended uses and equivalent technologies. A detailed comparison of VR101 with predicate Replens® is provided in a separate document, titled “Regulatory Comparison of the Predicate Device, Replens® Vaginal Moisturizer in Pre-Filled Applicators, with VR101”.

5.3 Study Participants

5.3.1 Inclusion Criteria for Participant Selection

Investigation Participants Must:

- Completely understand and sign the informed consent form (ability to read and understand the consent form in the English language).
- Be females 35 years of age or older.
- Express willingness to comply with the study visit schedule (see Table 4 in study procedures section).
- Over the course of the study:
    - Express willingness to abstain from the use of any vaginal moisturizers or lubricants or any other topically applied vaginal products not provided by study staff during VR101 or sham use, or during the Washout Period
    - Express willingness to abstain from the use of any HRT (hormone replacement therapy) or hormone-containing birth control products
    - Express willingness to abstain from use of any vaginal ring, diaphragm, cervical cap, or pessary products
- In the previous 60 days, have self-reported vaginal dryness that interferes with daily activities, which may include sexual intercourse

- Present with a VHI score of 22 or less, as scored by a trained clinician during the initial visit

NOTE: At least one-third of study participants must be menopausal (must self-report that they have not experienced a menstrual period in the last 12 months). If necessary to ensure this proportion is achieved, an inclusion criterion requiring that a participant self-report to being menopausal may be added as the study progresses.

5.3.2 Exclusion criteria for participant selection

Participants self-reporting any of the following will be ineligible for study entry:

- Current use of HRT (Hormone Replacement Therapy) or any hormone-containing birth control products.
- Vulvar or vaginal procedures (biopsies, radiation) in the last 3 months.
- Active vulvar or vaginal infections/lesions or complaints, as well as undiagnosed abnormal genital bleeding.
- History of chronic pelvic pain, interstitial cystitis, vulvar vestibulitis, pelvic inflammatory disease within the past 3 months.
- Known current, clinically evident cervical or vaginal infection.
- Participants who have given birth or terminated pregnancy in the past 6 weeks.
- Postpartum or post-abortion endometritis, unless symptoms resolved at least 3 months prior to study entry.
- Current persistent, abnormal vaginal bleeding.
- History of inability to place a vaginal ring.
- History of any abnormality of the vagina resulting in distortion of the vaginal canal or incompatibility with intravaginal ring placement.
- Body habitus or history of lower genital tract abnormalities or prior surgeries which may not allow the vagina to be appropriately accessed.
- Known or suspected allergy or hypersensitivity to polyurethanes or glycerol.
- Known current alcohol or illicit drug abuse.
- Participants who have not recovered from adverse events due to chemotherapy or radiation treatment for cancer.
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection of the urogenital tract, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Any condition that in the opinion of the investigator or study staff that would constitute contraindications to participation in the study or would compromise ability to comply with the study protocol.

- Current use of a vaginal ring, pessary, cervical cap or diaphragm unless willingness to discontinue for the study duration is expressed.
- Pregnancy or plans to become pregnant in the next 6 months.
- Current breastfeeding and inability or unwillingness to discontinue breastfeeding for the duration of the study.

NOTE: IUD (Intrauterine Device, e.g., ParaGard®) users may be enrolled provided they commit to exercising caution when removing VR101 as IUD strings have been noted to interfere with VR101 removal.

NOTE: Participants who have previously undergone anterior and/or posterior vaginal repair and have received a vaginal mesh implant may have difficulty placing VR101, although no safety issues with VR101 use in CI01 participants who had vaginal mesh implants were noted.

5.3.3 Point of Enrollment

Participants will be considered to be enrolled upon signing the Informed Consent Form and meeting all inclusion and exclusion criteria, including inclusion criterion requiring a VHI baseline score of 22 or less. See section 8.2 for further detail regarding the VHI baseline inclusion criterion. Randomization will occur during Visit #1, following a successful VHI assessment and prior to distribution of any study articles (i.e., VR101 or sham control devices).

5.3.4 Duration of Participation

Participants will be enrolled in the study for up to 25 weeks. This will consist of a crossover study, (4 weeks of VR101/sham use, 3-week washout period, 4 weeks of sham/VR101 use), then up to 13 additional weeks VR101 use in the open-label, long-term safety evaluation, followed by a follow-up questionnaire completed 1 week after the last VR101 device is removed.

Participants will be randomly assigned to either Group S1V2 or Group V1S2. Participants in Group S1V2 will complete the crossover study (11 weeks: 4 weeks sham followed by 3 weeks wash-out followed by 4 weeks VR101) and will continue to the long-term safety evaluation (10 additional weeks, including the final follow-up call). Participants in Group V1S2 will complete the crossover study (11 weeks: 4 weeks VR101 followed by 3 weeks wash-out followed by 4 weeks sham), and will participate in the long-term safety study (13 additional weeks of VR101 use plus a final follow-up call conducted 1 week after removal of the last VR101 device [14 weeks total]).

5.3.5 Participant Withdrawal/Discontinuation

Participants may voluntarily withdraw from the investigation for any reason at any time.

The plan for handling of incomplete efficacy study data sets (first 4 weeks of VR101 device or sham use) is described in sections 8.8 and 8.9.

If a participant discontinues VR101 use during the long-term safety evaluation, she may resume use of a fresh VR101 device at any time, provided enrollment has not been terminated. If the ring used prior to discontinuation was used for less than 5 days, then the week will need to be restarted. For example, if a participant in the safety study discontinues use of her 6th device on the 3rd day after its insertion, she will need to restart Week 6 with a fresh device, which will be inserted for the full 7 ± 2 days.

During the crossover study period, if a participant discontinues mid-week and restarts the study, the next ring must be inserted and the week will need to be restarted (similarly to the example given above), unless the ring was used for at least 5 days before the participant discontinued use. This criterion will also be applied to participants who begin a menstrual period during use, who will be instructed to remove the currently inserted ring and insert a new ring following cessation of menstruation. However, if a participant begins a menstrual period at any time during use of her 4th VR101 or sham control, she will be instructed to remove the ring, and restart with a 5th ring following cessation of menstruation. In this specific case, the participant's "28-day" efficacy evaluation actually would occur after using 5 devices instead of 4 (since it is not possible to obtain an unadulterated VHI assessment during menstruation).

Participants who report for a Study Visit during menstruation will be instructed to remove their current ring, and will re-start the study schedule per the above criteria.

NOTE: Participants who discontinue ring use mid-week and restart for any reason (including a menstrual period) will naturally deviate from the visit scheduling windows (e.g. 28±2 days) listed in Section 5.4.3. These events should be accurately recorded and documented, but do not need to be treated as formal Deviations from the Plan per Section 11. In Daily Diaries, participants will be asked to document the date and time of any such ring removal/discontinuation of use and the date and time the new ring was inserted.

All safety data will be used to test the primary safety hypothesis, except that partial ring uses will not be counted in the total number of rings used (see Endpoint 5). All participants will be automatically selected to participate in the safety portion of the investigation.

Participants who become pregnant during the study will be instructed to discontinue use of VR101 and will be dropped from the study. Study staff will refer any such participants to a clinical facility for follow-up. Efficacy datasets from these participants will be handled as described for incomplete efficacy study datasets in section 8.8 and 8.9.

When the last participant completes the crossover study and the blind is broken, participants in Group V1S2 will be contacted by study staff and asked to discontinue VR101 use and return any remaining study products (shams or VR101 devices) to the clinic at their earliest convenience.

5.3.6 Number of Participants

72 participants (36 at each study site) were enrolled in CI02 with a goal of at least 60 completing the efficacy evaluation (first 11 weeks and 6 study visits) and at least 30 completing the long-term safety evaluation. Based on our drop-out rate analysis (see Section 8.4), we calculate that continuation of at least 42 participants to the long-term safety evaluation will ensure that 30 will complete the entire study. All participants will be automatically selected to participate in the long-term safety portion of the investigation.

To ensure that 60 participants successfully complete the study (and that 30 participants successfully complete the long-term safety study), it will still be possible to enroll participants to replace drop-outs at any point during the study until 60/30 participants have successfully completed the study, provided that the crossover study blind has not yet been broken (although active recruitment may discontinue when the estimated enrollment is met as described above). Note that if additional sites are used, the requirement for the minimum number of patients at each site will be modified accordingly.

5.3.7 Estimated Time Needed to Enroll Participants

Between both study sites, we expect approximately 3 to 6 patients to be enrolled per week. Since 60 to 69 participants need to be enrolled, the time to complete enrollment is conservatively estimated at 10 to 23 weeks from the time of initiation of the investigation at the last site.

5.3.8 Total Study Duration

The clinical investigation will continue until at least 60 participants have successfully enrolled in and completed the efficacy portion of the study and at least 30 participants have successfully enrolled and completed the long-term safety evaluation. This is expected to occur between 8 and 11 months (35 and 48 weeks) from initiation of the investigation, assuming the last patient enrolled is randomly assigned to complete the safety study.

5.3.9 Procedures for the Replacement of Participants

As described above, additional participants will be enrolled to account for the maximum expected drop-out rate to ensure that at least 60 participants complete the efficacy portion of the study and at least 30 participants complete the safety portion of the study.

The handling of data from participants who do not complete the study is described in Sections 8.8 and 8.9.

VR101 safety data (recording and analyses of adverse events) will be included in the assessment of safety endpoints regardless of how long a participant remains in the study.

5.4 Procedures

5.4.1 Participant Screening

- Each work day, the schedule of any clinic associated with one of the facilities participating in the clinical investigation may be screened for patients who may meet the eligibility criteria. Potential participants' names will be communicated to the appropriate study staff who may contact them to determine their interest in participating in the study.
- Interested clinicians and nurses will notify staff of participating clinics of potential participants.
- Participant also may be recruited from clinics or by word of mouth, or in response to ads placed to inform the public of the opportunity to participate in the study.
- The study will be listed on the ClinicalTrials.gov website, which could also attract participants.

5.4.2 Participant Enrollment/Recruitment

- Interested women will be invited to learn more about this study. The clinical staff initially may meet and present the study to patients during their planned clinic visits. If an interested possible participant calls the study coordinator, the potential participant may be given information over the phone and emailed (or mailed) the informed consent form for review.
- The study information will be presented to potential participants and explained. Study Visit #1 will be scheduled if interest persists and the potential participant meets inclusion/exclusion criteria (all except for the baseline VHI assessment, which will be performed immediately prior to placement of the first ring). Staff may email the informed consent form (ICF) to the potential investigation participant for review before her scheduled visit.
- A signed copy of the informed consent form (ICF) will be provided to the participant.
- The ICF will be stored with the participant's record or as part of the required investigation documentation.

NOTE: Directions to study center locations and parking will be provided as necessary.

5.4.3 Visit Schedule and Description

Participants must return to the clinic for determination of VHI Scores on the schedule shown in Tables 4 and 5.

NOTE: In order to minimize scoring inconsistencies, each participant's VHI Score will be assessed by the same clinician each time her VHI is assessed, meaning that if a clinician is to complete the Visit 1 (baseline) assessment for a participant, the same clinician should be available for all subsequent exams that are part of the efficacy portion of the study (approximately 7, 28, 49, 56, and 77 days later). If this is not possible, deviations are acceptable, provided that measurements that affect the Primary Efficacy Hypothesis (Visits 1, 3, 4 and 6) are measured by the same clinician for a given participant.

NOTE: Participants will be instructed to refrain from vaginal intercourse 24 hours prior to each scheduled visit. If the participant reports to having vaginal intercourse in this time-period, she will be rescheduled for the next clinic day if possible.

NOTE: The "EOT" visit and "Final PC" described in Table 4 are copied from a previous Protocol revision and are not needed for participants completing the investigation per protocol. However, the EOT visit and Final PC may be used for participants who drop from the study in between scheduled Visits.

Table 4. Schedule of Events (GROUP V1S2, V – VR101, S – Sham Control)

Visit	1	2	PC[1]	PC	3	PC	4	5	PC	PC	6	PC	PC	PC	7	PC	8	PC	9	PC	EOT[2]	Final PC[5]
Day (Nominal)	0	7	14	21	28	35	49	56	63	70	77	84	91	98	105	112 119 126 133	140	147 154 161	168	175	Study Withdrawal [4]	7 Days Post Removal
Informed Consent	X																					
Assign Subject Number	X																					
I/E Criteria	X																					
Demographics	X																					
Height & Weight	X																					
Concomitant Therapy	X	X			X		X	X			X				X		X		X		X	
Contraception	X																					
Pregnancy Test	X				X		X				X				X		X		X		X	
Pre-Study Survey	X						X															
Medical History	X																					
Pre-Procedure Survey		X			X		X	X			X				X		X		X			
VHI Assessment	X[6]	X			X[6]		X[6]	X			X[6]				X		X		X		X	
pH Assessment	X	X			X		X	X			X				X		X		X			
Post – Removal Survey		X			X			X			X				X		X		X			
Randomization	X																					
Device Dispensing		X			X		X	X			X				X		X					
Device Insertion	V	V	V	V			S	S	S	S	V	V	V	V	V	V	V	V				
Post-Insertion Survey	X	X					X	X			X				X		X					
Adverse Events	X	X			X		X	X			X				X		X		X		X	
Diary Dispensing	X	X			X		X	X			X				X							
End of Use Survey					X						X								X			
Phone Call Survey			X	X		X			X	X										X		X
Phone Call Ring Insertion Reminder			X	X					X	X		X	X	X		X						
Returned Ring Collection[3]		X[3]			X[3]		X[3]	X[3]			X[3]				X[3]		X[3]		X[3]		X[3]	
Diary Collection/ Compliance		X			X		X	X			X											

[1] PC= Phone Call

[2] EOT= End of Treatment, whether premature or after completion of the investigation.

[3] The subject will return all rings that were expelled or were removed prior to the 5-7 days of use and could not be reinserted for any reason. See Section 5.4.3

[4] May be used for any study participants (V1S2 or S1V2) who withdraw from the study between scheduled Visits

[5] If the "EOT" visit occurs within 7 ± 2 days of final ring removal, the "Phone Call Survey" can be administered in person and an additional follow-up call is not needed

[6] The same PI/Sub-I needs to complete the VHI at least on Visits 1, 3, 4 and 6 if at all possible. See Section 5.4.3

Table 5. Schedule of Events (GROUP S1V2, S – Sham Control, V – VR101)

Visit	1	2	PC	PC	3	PC	4	5	PC	PC	6	PC	7	PC	8	PC	EOT[2]	Final PC[4]
Day (Nominal)	0	7	14	21	28	35	49	56	63	70	77	84 91 98	105	112 119 126 133	140	147	Study Withdrawal 3	7 Days Post VR101 Removal
Informed Consent	X																	
Assign Screening Number	X																	
I/E Criteria	X																	
Demographics	X																	
Height & Weight	X																	
Concomitant Therapy	X	X			X		X	X			X		X		X		X	
Contraception	X																	
Pregnancy Test	X				X		X				X		X		X		X	
Pre-Study Survey	X																	
Medical History	X																	
Pre-Procedure Survey		X			X		X	X			X		X		X			
VHI Assessment	X[1]	X			X[1]		X[1]	X			X[1]		X		X		X	
pH Assessment	X	X			X		X	X			X		X		X			
Post-Removal Survey		X			X			X			X		X		X			
Randomization	X																	
Device Dispensing		X					X	X			X		X					
New Device Insertion	S	S	S	S			V	V	V	V	V	V	V	V				
Post-Insertion Survey	X	X					X	X			X		X					
Adverse Events	X	X			X		X	X			X		X		X		X	
Diary Dispensing	X	X					X	X			X		X					
End of Use Survey					X						X				X			
Phone Call Survey			X	X		X			X	X						X		X
Phone Call Ring Insertion Reminder			X	X					X	X		X		X				
Returned Ring Collection[2]		X			X		X	X			X		X		X		X	
Diary Collection/ Compliance		X			X			X			X							

[1]The same PI/Sub-I needs to complete the VHI at least on Visits 1, 3, 4 and 6 if at all possible. See Section 5.4.3
[2] The subject will return all rings that were expelled or were removed prior to the 5-7 days of use and could not be reinserted for any reason. See Section 5.4.3
[3] May be used for any study participants (V1S2 or S1V2) who withdraw from the study between scheduled Visits
[4] If the "EOT" visit occurs within 7 ± 2 days of final ring removal, the "Phone Call Survey" can be administered in person and an additional follow-up call is not needed

Follow-up phone calls will be conducted weekly in some weeks where the participant does not return to the clinic (days 14, 21, 63 and 70). Follow-up phone calls will also be conducted on day 35 and 147 (if applicable). The follow-up phone calls will be used to ask survey questions regarding their experience with the ring, as well as to remind participants of their responsibilities per their signed ICFs.

On days 84, 91, 98, 112, 119, 126, 133, 147, 154 and 168 no survey data will be collected, but participants will be given a reminder by phone to remove the VR101 and insert a new one.

Visit 1/4 - First Ring Insertion

NOTE: If this is a participant's first visit, the baseline VHI assessment and IVR placement must occur on the same day. If the baseline VHI assessment and first IVR placement attempt does not occur within 30 days of initial screening procedures, determination of participant's eligibility must be re-reviewed. Participants will be asked to complete a Pre-Study survey that will gather general demographic information as well as ask questions about vaginal dryness and the effects on sexual activity.

1. Assign a unique screening identifier to each participant (different from the Participant Number) and complete initial screening procedures.
2. Participants will complete a Pre-Study Survey (Visit 1) or a Pre-Procedure Survey (Visit 4).
3. Participants will be asked to provide a urine sample for a pregnancy test.
4. Participants will undergo a brief vaginal health assessment which will include a pH test and assignment of VHI scores (see Table 6). During Visit 1, if a participant is assigned a VHI score of 22 or lower (and met all other inclusion/exclusion criteria), she will be enrolled in the study and randomized. The participant will be assigned the next available (lowest remaining) Participant Number.
5. Enrolled participants will be provided with a package of either at least 6 each VR101 devices or at least 6 each sham controls (one for each of the first 4 weeks and at least 2 spares) with printed instructions for use. During Visit 1, the Participant will be given a package containing the Participant Number followed by the letter "A" (for example Participant 1 will be given a package labeled "1A"). During Visit 4, the Participant will be given a package containing the Participant Number followed by the letter "B" (for example Participant 1 will be given a package labeled "1B"). Participant numbers will be pre-randomized by the Sponsor, and only the Sponsor will have access to the randomization schedule. No additional information, verbal or otherwise, will be provided by the clinician to participants on the use of the device.
6. Enrolled participants will be shown to a private clinic area or restroom to self-insert one of the devices from package "A" (Visit 1) or "B" (Visit 4).
7. After insertion, participants will be asked to complete a Post-Insertion Survey that queries their first impressions of the IVR and the insertion process. If a participant has difficulty with placement, she can choose to not place the ring and will be withdrawn from the study. The first ring will remain in the vagina for 7 ± 2 days.
8. Participants will be given a daily diary to complete and return to study staff at each subsequent study visit. The diary will request information on comfort of device use during daily activities and symptoms of vaginal dryness.

NOTE: If the IVR is expelled during the 7-day investigation period, the participant will be asked to rinse it using tap water and reinsert unless it is not appropriate to reinsert the expelled ring (e.g., lost in toilet, soiled). If participant is unable or unwilling to reinsert the expelled ring, she will be asked to store it, if possible, in a provided re-sealable bag and bring it to her next clinic visit. If she is unable or unwilling to reinsert the expelled ring, she will be asked to insert a new ring. Participants will be instructed to document this event in the daily diary.

Visit 2/5 - Second Ring Insertion

1. Participants will return to the clinic on day 7/56 (± 2 days) and submit completed daily diaries.
2. Participants will be asked to report any Adverse Events (AEs), whether or not they feel they were related to use of the investigational device. AEs will be recorded on the Adverse Event Form (Attached).
3. Participants will be asked to complete a Pre-Procedure Survey.
4. Participants will undergo a brief vaginal health assessment that will include a pH test and assessment of Vaginal Health Index (VHI) (see Table 6).
5. Participants will be instructed to remove the ring per the instructions for use and without clinician input, and will be asked to complete a post-removal survey. The survey will include a comments section for users to provide feedback on the instructions for use and any steps that were difficult to understand.
6. Participants will be asked to insert a new ring per the instructions for use and without clinician input, and to complete a post-insertion survey.
7. This ring (VR101 or sham control), followed by a third and fourth device will be used consecutively, each to remain in the vagina for 7 ± 2 days.

Visit 3/6 – Final Crossover Arm Ring Removal

1. Participants will return to the clinic on day 28/77 (± 2 days) and submit completed daily diaries.
2. Participants will be asked to report any Adverse Events (AEs), whether or not they feel they were related to use of the investigational device. AEs will be recorded on the Adverse Event Form (Attached).
3. Participants will be asked to complete a Pre-Procedure Survey.
4. Participants will undergo a brief vaginal health assessment that will include a pH test and assessment of Vaginal Health Index (VHI) (see Table 6).
5. Participants will be instructed to remove the ring per the instructions for use and without clinician input, and will be asked to complete a post-removal survey.
6. Participants will be asked provide a urine sample for a pregnancy test.
7. Participants will be asked to complete an End-of-Use survey.

8. During Visit 6, the Participant will be given a package containing the Participant Number followed by the letter "C" (for example Participant 1 will be given a package labeled "1C") regardless of her randomization status. This package will contain 12 each VR101 devices (one for each week and 3 spares) and will be instructed to insert a new ring, again per the instructions for use and without clinician input.
9. Participants will be asked to complete a Post-Insertion survey.
10. During Visits 3 and 6, participants will be asked to return any additional unused devices (spares) left over from the previous package.
11. Devices administered will be used consecutively, each to remain in the vagina for 7 ± 2 days.

Final Visit (can be used for Participants who withdraw from the study between scheduled Visits)

1. When the crossover study blind is broken, V1S2 participants still using VR101 will be contacted and asked to discontinue VR101 use. A visit will be scheduled for the participant to return study products and disclose any Adverse Events or concomitant mediation changes.
2. During the Visit, participants will be asked to provide a urine sample for a pregnancy test.

Visit 7 (all)/Visit 8 (V1S2 only) - Long-Term Safety Visit

1. Participants still enrolled in the study will return to the clinic on day 105/140 (± 2 days).
2. Participants will be asked to report any Adverse Events (AEs), whether or not they feel they were related to use of the investigational device. AEs will be recorded on the Adverse Event Form (Attached).
3. Participants will be asked to complete a Pre-Procedure Survey.
4. Participants will undergo a brief vaginal health assessment that will include a pH test and assessment of Vaginal Health Index (VHI) (see Table 6).
5. Participants will be instructed to remove the ring per the instructions for use and without clinician input, and will be asked to complete a post-removal survey.
6. Participants will be asked to provide a urine sample for a pregnancy test.
7. Participants will be asked to insert a new ring per the instructions for use and without clinician input, and to complete a post-insertion survey.
8. This device and 3 additional VR101 devices will be used consecutively, each to remain in the vagina for 7 ± 2 days.
9. During Visit 8, V1S2 participants will be given 4 additional VR101 devices

Visit 8 (S1V2) or Visit 9 (V1S2) - Final Long-Term Safety Visit

1. Participants will return to the clinic on day 140 (S1V2) or day 168 (V1S2) (± 2 days) .
2. Participants will be asked to report any Adverse Events (AEs), whether or not they feel they were related to use of the investigational device. AEs will be recorded on the Adverse Event Form (Attached).
3. Participants will be asked to complete a Pre-Procedure Survey.
4. Participants will undergo a brief vaginal health assessment that will include a pH test and assessment of Vaginal Health Index (VHI) (see Table 6).
5. Participants will be instructed to remove the ring per the instructions for use and without clinician input, and will be asked to complete a post-removal survey.
6. Participants will be asked to provide a urine sample for a pregnancy test.
7. Participants will be asked to complete an End-of-Use survey.
8. Participants will be asked to return all unused rings to the clinic.

5.4.4 Assessment of Vaginal Health Index (VHI)

The following instructions will be provided to clinical personnel:

- Insert speculum and open the blades sufficiently to expose the cervical os. Secure the position of the speculum.
- Complete Vaginal Health Index Assessment Form (see Table 5 below for VHI scoring) for the appropriate visit number and study participant ID.
- Sample vaginal fluid for pH measurement (exact method to be documented in the CI02 clinical protocol).
- Remove speculum.
- Ensure that all required fields on the VHI Score form are completely filled-in.

Table 6. Scale for Scoring Individual Vaginal Health Index Components to arrive at a VHI Score

	Vaginal Health Index Component Score				
VHI Component	**1**	**2**	**3**	**4**	**5**
Elasticity	None	Poor	Fair	Good	Excellent
Fluid Volume	None	Scant amount (vault not entirely covered)	Superficial amount (vault entirely covered)	Moderate amount	Normal amount
Epithelial Integrity	Petechiae noted before contact	Bleeds with light contact	Bleeds with scraping	Not friable, thin epithelium	Normal
Moisture (Coating)	None Surface inflamed	None Surface not inflamed	Minimal	Moderate	Normal
pH	6.1 or above	5.6-6.0	5.1-5.5	4.7-5.0	4.6 or below

All Vaginal Health Component scores are determined by clinicians receiving the same training in the assessment and scoring of VHI components. VHI component scores shall be assessed according to the following metrics (Bachmann 1991):

Elasticity – Elasticity of the tissue as determined by the resistance of stretch noted with digital palpation

Fluid Volume – The quantity of secretions pooled in the posterior vaginal vault

Epithelial Integrity – Epithelial integrity as determined by color, rugation and friability of the vaginal surface with speculum insertion

Moisture – The appearance and spread of the secretions coating the vaginal vault

5.4.5 Participant Assessment of Vaginal Dryness Relief (Endpoint 2 and Exploratory Endpoints)

The following 4 questions will be asked at each clinical visit as part of each Pre-Procedure Survey. These questions will also be asked during each follow-up call.

1. *Think about the last 7 days. In how many of those days did you experience any vaginal dryness?* ("Vaginal Dryness Frequency")
2. *On average, how would you rate your vaginal dryness in the last 7 days?* ("Weekly-Averaged Severity of Vaginal Dryness")

3. *On average, how would you rate your worst day of vaginal dryness symptoms?* ("Peak Severity of Vaginal Dryness")
4. *How would you rate your vaginal dryness in the last 24 hours?* ("24-hour vaginal dryness severity")

Possible responses for question 1 are integers from 0 to 7 (assuming the ring was in place for exactly 7 days), while possible responses for questions 2-4 are as follows:

"I have not experienced vaginal dryness"	(assigned a score of 0)
"Mild"	(assigned a score of 1)
"Moderate"	(assigned a score of 2)
"Severe"	(assigned a score of 3)

Responses to Question 2 prior to ring insertion and to Question 4 following use of the first VR101 for 7 days will be used to assess the validity of Claim 1.

5.4.6 Additional Participant Surveys (Exploratory Endpoints unless noted)

At each clinical visit and in daily diaries, participants will be given statements and asked to score their level of agreement or disagreement as follows:

"Disagree completely"	(assigned a score of -4)
"Disagree a lot"	(assigned a score of -3)
"Disagree somewhat"	(assigned a score of -2)
"Disagree a little"	(assigned a score of -1)
"Neither agree nor disagree"	(assigned a score of 0)
"Agree a little"	(assigned a score of 1)
"Agree somewhat"	(assigned a score of 2)
"Agree a lot"	(assigned a score of 3)
"Agree completely"	(assigned a score of 4)

The following statements will be presented as part of clinical visit surveys (see Section 5.4.3 for clinical visit schedule). Only statements pertinent to non-exploratory endpoints are detailed below. Each survey will contain additional statements and questions designed for exploratory evaluations of VR101 use. Refer to the survey Case Report Forms (Attached), for the complete set of survey questions.

Post-Removal Survey

The ring was easy to use by following the provided instructions (Data from Visit 2 will be used to Assess Claim 2)

Daily Diary

The statement "*the ring was comfortable to me today"* will be included as part of a daily diary (used to assess the validity of Claim 3).

5.4.7 Device Insertion Procedures

VR101/Sham Control Placement

Instructions for distribution of sham rings and VR101 devices to study participants follow.

- Provide enrolled participants with a package of either at least 6 each VR101 devices or at least 6 each sham controls (one for each of the first 4 weeks and at least 2 spare rings) with printed instructions for use. The outer packaging will contain a unique identifier that will identify the ring as a VR101 device or sham control that is only known by the study coordinator or his or her authorized representative.
- Record the total number of rings and their Identifiers given to the participant in the Device Accountability Log.
- Query participant to complete the post-insertion questionnaire.
- Instruct and review use of Daily Diary. Instruct participant to complete and bring Diary to each subsequent investigation visit. Remind participant that both Sections A and B of the Daily Diary need to be completed.
- If a ring is accidentally expelled during the study, the participant will be reminded to follow the instructions for use, which allow it to be rinsed it in the sink under tap water and reinserted, unless it is not appropriate to reinsert the expelled ring (e.g., because it was lost in toilet, was soiled). If participant is unable or decides not to reinsert the expelled ring, she will be asked to store it, if possible, in the provided re-sealable bag and bring it to her next clinic visit. If she is unable or decides not to reinsert the expelled ring, she will be asked to insert one of the spare rings sent home with her. Use of spare rings and the circumstances leading to such use will be recorded in the Daily Diary.
- If a participant needs to use more than two spare rings between any two visits, she will need to return to the clinic to receive an additional ring. The ring will be provided by the Sponsor, as they are the only party aware of whether a sham or VR101 ring needs to be provided.
- Instruct the participant to return any unused study rings (VR101s and shams) in their original packaging to the investigation site.

Device Insertion and Removal Instructions (as given to study participants, will be identical for VR101 and shams)

1. Wash and dry your hands thoroughly.
2. Remove ring from its pouch.
3. Before inserting, find a position that is comfortable. You can insert the ring while lying down, squatting, or standing with one leg up, whatever position is most comfortable for you.
4. Hold the ring between your thumb and first finger, pressing opposite sides of the ring together. You may want to twist it into a figure 8.
5. It may help you to hold open the folds of skin around your vagina with your opposite hand while inserting the ring.
6. Place the tip of the ring in the vaginal opening and then push the folded ring gently into your vagina. Push the ring up and toward your back. Do not use any lubrication.
7. If you feel any discomfort, the ring probably is not inserted far enough. Try gently pushing the ring further into your vagina. The ring will not get lost in your body.
8. When you are finished, wash and dry your hands thoroughly.

Return any rings that you were unable to place for any reason to the clinic at your next visit. Before returning a ring to the clinic, place in the original foil-lined pouch if available. If not, place in a zip lock-type bag.

Warning: Do not use the ring if it appears to be damaged and/or if the package appears open or damaged.

Warning: Do not re-insert a ring that you removed or that was expelled if it appears damaged or contaminated. You may wash it in clean water and re-insert it if it is clean. Or, use a new ring. Return any rings you chose not to re-insert to the clinic at your next visit.

Device Removal

Remove the ring after 7 days of use.

1. Wash and dry your hands.
2. Choose the position that is most comfortable for you.
3. Put you index finger into your vagina and hook it through the ring and gently pull downward and forward to remove the ring.
4. Discard the used ring in the trash and out of reach of children and pets. Do not flush the ring in the toilet.
5. Insert a new ring after removal of the used ring.

Warning: Do not re-insert a ring that you removed or that was expelled if it appears damaged or contaminated. You may wash it in clean water and re-insert it if it is clean. Or, use a new ring. Return any rings that were unable to be replaced to the clinic during your next visit. Before returning a ring to the clinic, place in the original foil-lined pouch or in a zip lock-type bag.

If you have any questions or concerns call the study coordinator (phone number to be included with packaging).

5.4.8 Interim Follow-Up Call Schedule

Each participant will be contacted by phone on days 14, 21, 35, 63, 70 and either day 147 (V1S2 completer), day 175 (S1V2 completer) or 7±2 days following removal of her last ring (if discontinued prior to day 147), to assess their medical condition and to complete a short questionnaire regarding their experience with ring use. If a participant is discontinued prior to completion of the safety arm and returns to the clinic for her final visit within 7±2 days following removal, all information can be collected during this visit and an additional follow-up call is not needed. For calls during ring use (days 14, 21, 63 and 70), participants will also be reminded to remove their current ring and insert the new ring on these days.

5.4.9 Terminal Follow-Up Procedure

One week after the last VR101 or sham is removed, each participant will be contacted to assess her medical condition and to complete the study questionnaire. Each participant will also be reminded that she may contact the clinic at any time after the study if she is experiencing any discomfort that she believes may be related, directly or indirectly, with use of the VR101 or the sham.

5.4.10 Factors That May Compromise the Outcome of the Investigation

Assessment of Efficacy (VHI scoring)

Training in the assignment of Vaginal Health Index (VHI) scores will be provided to all PIs to assure consistency of clinician assessments. In order to minimize the effects of differences in the assignment of VHI Scores, each participant's VHI Scores will be assigned by the same clinician each time her VHI is assessed, meaning that if a clinician completes the Visit 1 (baseline) assessment for a participant, the same clinician must be available for all subsequent exams in the first 77 days of the study. Consequently, the relative VHI Scores associated with each participant's use of VR101 or the sham control, and the comparison between the two ΔVHI scores, will not be compromised. Further, to minimize bias, although the clinician conducting the VHI assessment may be able to see the inserted ring during VHI assessments, they will not likely be able to tell whether or not a sham control or VR101 is inserted. Clinicians performing the assessment will not be allowed to requisition rings from storage or distribute them to the patient to assure they are appropriately blinded to the identity of the ring used by each participant.

Study Compliance

If participants do not adhere to the indicated schedules (i.e., device use, daily diary completion, visits to the clinic), then the data collected in the investigation may be compromised or incomplete. Therefore, every attempt will be made to assure compliance with the visit schedule. The treatment of incomplete data sets is addressed in Sections 8.8 and 8.9.

Participant Use of Products Excluded from the Study

Neither clinical personnel nor the Sponsor will have the ability to directly monitor participants and ensure that they abstain from using products defined in the exclusion criteria (e.g., hormone-containing therapies, other vaginal rings). The Diaries and communication between participants and study personnel will be used to estimate adherence to the restrictions on use of prohibited products.

5.5 Monitoring Plan

The investigation will be monitored per J3 BIO's internal Good Clinical Practice (GCP) documents. The monitoring schedule is as follows:

Initiation of the Investigation

Each PI and Site will be visited by the Study Monitor and approved by the Sponsor and Study Monitor and training provided on the requirements of the study before clinical samples may be provided to the PI.

Interim Monitoring Visit

Interim monitoring of each site will occur after approximately 3 to 5 participants have enrolled in the study at each site (see Appendix A, below, for Monitoring Plan), and again after 20 to 25 participants have enrolled at each site, and after 20 to 25 participants have completed at least 4 weeks of the study at each site. An additional monitoring visit will be conducted after the last participant at each site has completed the crossover study. Additional visits may be scheduled to assure assessments are conducted over the duration of the study.

Monitoring Closeout Visit

The closeout visit will occur at each site following completion of the final clinical visit. Additional monitoring may be scheduled, at the discretion of the Sponsor, if protocol deviations or significant adverse events are reported or otherwise identified.

NOTE: Study monitors must not be aware of any participant randomization assignments (maintained by the Sponsor) at any time before the Study is opened (See Section 9)

5.6 Labeling

Device labeling is provided below for VR101 devices. VR101 labels will include the wording "for investigational use only" and other wording and markings to assure compliance with FDA and ISO 14155 requirements, as appropriate.

Each VR101 device is individually sealed in a polyethylene-lined foil pouch and labeled with CI02-LBL01 Device Label and Identifier. The sealed pouch is then placed in a polyolefin zip-lock bag and the insertion instructions are adhered to the outside of the zip-lock bag. Clinical staff (other than the physician assessing VHI scores) may distribute the bags containing the VR101 packaged devices in sealed pouches to study participants. The draft label and draft instructions for use are shown below.

Instructions for use and labeling of sham rings will be identical to those provided for VR101 devices. As described above, bundles of 6 each VR101 devices or sham controls will be given to participants at the beginning of the crossover study. Only the Sponsor or his or her authorized representative will have knowledge of which packaging identifiers correspond to either VR101 or the sham control. The identity of administered rings will not be disclosed to any clinicians who collect patient or ring (VR101 or sham) data.

Investigational VR101 Label (LBL 001 R00)

VR101 Vaginal Lubrication Ring
Manufactured by: J3 Bioscience, Inc.,
615 Arapeen Drive, Suite 310, Salt Lake City, Utah 84108

VR101 is a personal lubrication device for vaginal application intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication.

CAUTION: Investigational device limited to investigational use only.
CONTRAINDICATIONS: Use is restricted to patients enrolled in VR101 Clinical Study.
WARNINGS: For vaginal use only. VR101 is not a contraceptive, does not contain a spermicide and does not protect from any sexually-transmitted infections. Keep out of reach of children. Do not ingest or place in mouth. If vaginal irritation occurs, discontinue use. If symptoms persist, contact your clinician. If pregnant or breast feeding, consult your healthcare provider before use.

Store at room temperature. LBL 001 R00 2017-03
Expiration Date:
SEE INSTRUCTIONS FOR USE

Investigational VR101 Instructions for Use (LBL 002 R00)

VR101 Insertion Instructions

Prior to use, inspect each package for damage.
Do not use if package or device appears damaged.
Read ALL Instructions before inserting and removing VR101.

1. Wash and dry your hands thoroughly.
2. Remove ring from its pouch.
3. Before inserting VR101, find a position that is comfortable. You can insert the ring while lying down, squatting, or standing with one leg up, whatever position is most comfortable for you.
4. Hold the ring between your thumb and first finger, pressing opposite sides of the ring together. You may want to twist it into a figure 8.
5. It may help you to hold open the folds of skin around your vagina with your opposite hand while inserting the ring.
6. Place the tip of the ring in the vaginal opening and then push the folded ring gently into your vagina. Push the ring up and toward your back. Do not use any lubrication.
7. If you feel any discomfort, the ring probably is not inserted far enough. Try gently pushing the ring further into your vagina. The ring will not get lost in your body.
8. When you are finished, wash and dry your hands thoroughly.

Return any rings that you were unable to place for any reason to the clinic at your next visit.
Before returning a ring to the clinic, place in the original foil-lined pouch if available. If not, place in a zip lock-type bag.
Warnings:

- Do not use the ring if it appears to be damaged and/or if the package appears open or damaged.
- Do not re-insert a ring that you removed or that was expelled if it appears damaged or contaminated. You may wash it in clean water and re-insert it if it is clean. Or, use a new ring. Return any rings you chose not to re-insert to the clinic at your next visit.

VR101 Removal Instructions

Remove each VR101 ring after 7 days of use.

1. Wash and dry your hands.
2. Choose the position that is most comfortable for you.
3. Put you index finger into your vagina and hook it through the ring and gently pull downward and forward to remove the ring.
4. Discard the used ring in the trash and out of reach of children and pets. Do not flush the ring in the toilet.
5. Insert a new ring after removal of the used ring, according to the instructions provided above.

Warning: Do not re-insert a ring that you removed or that was expelled if it appears damaged or contaminated. You may wash it in clean water and re-insert it if it is clean. Or, use a new ring. Return any rings that were unable to be replaced to the clinic during your next visit. Before returning a ring to the clinic, place in the original foil-lined pouch or in a zip lock-type bag.

If you have any questions or concerns call the study coordinator:

In Utah: 801-542-8190 x111 In Idaho: 208-377-8653 x111

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6 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

6.1 Need for the Proposed Clinical Investigation

The Sponsor is not aware of any clinical studies that have been or are currently being conducted to evaluate the safety or effectiveness of a vaginal lubrication ring similar to the proposed VR101 devices. To fulfill the premarket requirement for the establishment of safety and efficacy equivalent to that of a predicate device for devices categorized similarly to VR101 before these devices may be legally marketed in the US, this study is proposed. Study data may also be used to satisfy the requirements of the Medical Devices Directive to support CE Marking of the device.

6.2 Successful Completion of Pilot Study

A pilot clinical investigation of VR101 was successfully completed in May 2014. Refer to Section 2.4 for a brief summary of this study and to the summary of the Clinical Investigation CI01 Final Report.

6.3 Clinical Investigation and 510(k) Clearance of Predicate Device

The predicate device was cleared by the FDA on August 17, 2010 after review of K101241, submitted by Lil' Drug Store Products, Inc. The 510(k) summary for this device, Replens® Long-Lasting Vaginal Moisturizer (in pre-filled applicators), references the following clinical investigations, which were conducted on Replens® Long-Lasting Vaginal Moisturizer, not necessarily provided in and delivered by applicators. The studies disclosed in the 510(k) summary are identified in the table below.

Citation	No. Patients Enrolled (Replens)	Study Design*	Dosage Regimen	Duration
Bachmann et al	89	D-B, X-over	2.5 g per day	5 days
Bachmann et al	54	Open	2.5 g, 3 x weekly	12 months
Zinny and Lee	26	D-B, parallel	2.5 g alternate nights	4 weeks
Young et al	30	Open	2.5 g, 3 x weekly, plus option of additional application prior to intercourse.	12 months
Nakamura	10	Open, X-over between treatment durations	2.5 g daily	1-5 days

Citation	No. Patients Enrolled (Replens)	Study Design*	Dosage Regimen	Duration
Whitehead	32	D-B, X-over	2.5 g, 3 x weekly plus option of additional application prior to intercourse.	8 weeks
Nachtigall	15	Open, parallel	2.5 g, 3 x weekly	3 months
Gelfand and Wendman	25	Open	2.5 g, 3 x weekly, plus option of additional application prior to intercourse.	3 months

* D-B = double-blind; X-over = cross-over design

6.4 Justification of Study Endpoints

Endpoint 1 (Change in VHI for participants using VR101 compared with the change in VHI resulting from use of the sham rings), was selected because it allows for a quantitative, objective endpoint evaluated by a qualified clinician blinded to the treatment. Also, VHI is a measure of lubricant efficacy which was used to assess the efficacy of the predicate device (see references in above table), allowing J3 BIO to evaluate the substantial equivalence of VR101 to the predicate device for 510(k) premarket notification purposes. Because VHI scores have been established as an acceptable metric for evaluating the efficacy of devices intended to treat symptoms of vaginal dryness (e.g., K101241), it would be logical to use this endpoint to assess the effectiveness of the new VR101 device and establish its substantial equivalence to the predicate Replens devices. By comparing baseline-adjusted VHI scores we allow each participant to serve as her own control in order to show that VR101 provides superior vaginal dryness relief to that of a sham ring which does not include lubricant, and can rule out any positive lubricating or moisturizing effects attributed to the insertion of the unfilled sham rings.

Endpoints 2 to 4 were selected as the participant is the best assessor of her physical comfort and her ease of use the device. Objective measures of vaginal dryness may be better at quantifying responses, but if the user does not sense and report an improvement of her condition, then the treatment may not be clinically useful or necessary or meet user needs or intended uses.

Endpoint 5 was selected (proportion of serious device-related adverse events) to assure that the device can be used safely and that benefits of device use outweigh risks.

7 RISKS AND BENEFITS OF VR101 AND CI02

7.1 Risk Management

J3 BIO employs risk management practices to meet the requirements of ISO 14971.

7.2 Clinical Hazard Assessment (CHA)

A Clinical Hazard Assessment was performed prior to initiating the pilot clinical investigation (CI01). A summary of this assessment, which has been updated to account for new information gained in the pilot investigation, can be found in the Investigator's Brochure, IB02.

7.3 Risk-Benefit Ratio

A benefit/risk assessment is included the Investigator's Brochure, IB02. The assessment concludes that "The benefits derived from the use of lubricants and moisturizers to treat vaginal dryness far outweigh the complications and risks identified in the literature. The major drawback to the use of lubricants is that they must be reapplied on a consistent basis to be effective and their application interferes with spontaneity of sex."

8 STATISTICAL CONSIDERATIONS

8.1 Summary of Statistical Methods

The hypotheses of the clinical investigation are detailed in Section 4.2. For Primary Efficacy and Validation of Claim 1, the null hypothesis will be rejected based on a two-tailed Student's t-test ($\alpha = 0.05$) or an appropriate non-parametric two-tailed test if the data do not appear to be normally distributed.

The remainder of hypotheses will be tested using the 95% confidence interval associated with a proportion of events (e.g. SADE occurrence per number of devices used, proportion of favorable survey responses).

8.2 Sample Size Determination based on Statistical Power to Show Efficacy

A mean power analysis was performed to determine the number of participants required to demonstrate superiority in ΔVHI scores (baseline VHI minus adjusted VHI) between VR101 and a sham ring (improvement of vaginal dryness symptoms).

In the pilot clinical investigation of VR101, the mean and standard deviation of paired differences in VHI composite scores was 1.19 ± 2.35. This composite score included an estimate of scaled pH (see Section 5.4.4) which was a value estimated based on values obtained on day 14 (following consecutive use of two VR101 devices, each for 7 consecutive days), and day 0 (baseline). These data represent the data collected in the pilot study that are most similar to the proposed Primary Efficacy Endpoint, but conservatively assume the sham ring does not affect

VHI scores.

The maximum VHI score is 25 (there are 5 components of the VHI, each of which can be assigned a score of a maximum of "5"). Participants with an initial baseline VHI of 23 or higher will be excluded from study enrollment, as these participants' scores indicate that they do not, from an objective assessment (VHI) standpoint, present with symptoms indicative of vaginal dryness- a majority (at least 3 of 5) of VHI component scores are "perfect" "5"s. With the exclusion from the CI01 data set of participants' VHI scores who were 23 or higher at the initiation of the study, the mean and standard deviation of 14-day ΔVHI scores recorded in CI01 was 1.78 ± 2.14. A sample size of 60 participants receiving both sham rings and active devices in the proposed crossover investigation will have 99% power to detect a difference in ΔVHI means of 1.78 assuming a standard deviation of differences of 2.14, using a paired t-test with a 0.05 two-sided significance level.

If use of the sham rings in CI02 results in a VHI improvement that is 50% as great (ΔVHI=0.89), as that obtained for use of the VR101 in the pilot study (ΔVHI=1.78), and use of VR101 results in the same improvement in VHI scores (ΔVHI=1.78) recorded in the pilot CI01 study, a sample size of 60 participants using both sham rings and VR101 devices in the proposed crossover investigation will have 88% power to detect a difference in ΔVHI means of 0.89, assuming a standard deviation of differences of 2.14, using a paired t-test with a 0.05 two-sided significance level (results obtained using nQuery Advisor 7.0; MOT1-1 module).

Thus, a sample size of 60 participants completing the study will be used for CI02, where the required power is 80% (and the theoretical, calculated power achieved is 88% under the assumptions provided above).

The number of participants in the long-term safety study will be at least 30.

8.3 Statistical Power of Proposed Clinical Investigation to Demonstrate Device Safety

If, during the course of CI02, 30 participants use a total of 13 each VR101 devices (390 VR101 devices, total) during the long-term safety portion of the study, and an additional 30 participants use a total of 4 VR101 devices during the 4-week crossover efficacy portion (120 VR101 devices, total), then, at the conclusion of CI02, a total of 553 VR101 devices will have been used (510 total uses of VR101 devices in CI02, plus an additional 43 total VR101 devices already used in CI01 [with no SADEs observed in CI01]). Note that this total number of devices used does not account for VR101 devices used for less than 5 days whose data will not be used in assessing efficacy, but whose data will be included in the sample of devices used to assess safety. So, it is likely that the number of VR101 device uses evaluated for safety will exceed 553.

If 2 SADEs occur out of a total 510 VR101 devices used according to instructions in the proposed investigation, then we will be able to rule out SADE rates greater than 1 event per 100 devices with 95% confidence. The 95% confidence interval for 2 events in 510 devices is (0.00, 0.01) (exact test, Minitab 17).

However, if no SADE is observed during the entirety of CI02 (0 events/510 devices), as expected, we will be able to rule out a SADE rate greater than 0.6 events per 100 devices with 95% confidence. The 95% confidence interval for 0 events in 510 observations is (0.000, 0.006) (exact test, Minitab 17).

Further, if no SADE is observed during the entirety of CI02 and CI01 (0 events/553 devices), as expected, we will be able to rule out a SADE rate greater than 0.5 events per 100 devices. The 95% confidence interval for 0 events in 553 observations is 0.000 (0.000, 0.005) (Minitab 17).

8.4 Expected Drop-Out Rates

NOTE: The first paragraph below contains out-of-date information, as of this Revision, but is included for reference.

During the pilot investigation (CI01), one participant missed multiple study visits and discontinued the VR101 treatment regimen. However, the participant eventually restarted and successfully completed the investigation, meaning that the drop-out rate for CI01 was 0%. Statistically, if the dropout rate is "0" for a sample size of 21, we can then rule out any drop-out rates higher than 14.6% with 95% confidence (upper bound of the exact Blyth-Still-Casella confidence interval for the proportion 0/21). However, since CI02 requires longer continued participant involvement than CI01, it is possible that the drop-out rate for enrolled participants in CI02 may even exceed 14.6%. We have assumed a 14.6% dropout rate to estimate the number of participants to enroll in the proposed investigation.

The 95% confidence interval used above still underestimated the drop-out rate due to the differing enrollment durations of CI01 and CI02. During the crossover study, which lasted for 11 weeks (per participant), 11 of 72 participants withdrew from the study (1.39% of initial enrollment per week [average], 0.70-2.47% per week [95% CI]. Assuming that half of the participants will participate in the long-term safety study for 9 weeks (Group S1V2) and the remaining half will participate for 13 weeks (Group V1S2), continuation of at least 42 total participants will ensure, with 95% confidence, that 30 participants will complete the long-term safety evaluation (13 consecutive weeks of VR101 use).

Since participants will need to be re-consented when this protocol revision takes effect, the number of additional dropouts (not accounted for by the calculation above) when participants are presented with the new Informed Consent Form is unknown. Therefore, we will offer

participation in the long-term safety study to all available participants (up to 61) to ensure that the goal, of 30 participants using VR101 continuously for 13 weeks in the safety portion of the investigation, is met.

8.5 Pass/Fail Criteria of the Clinical Investigation

The clinical investigation will be considered a success if the null hypotheses for the primary efficacy and safety endpoints are rejected as defined in Section 4.2.1 and 4.2.2, respectively. If these two null hypotheses are rejected, reasonable safety and efficacy of VR101 following long-term sequential use will be established and substantial equivalence of VR101 with the predicate Replens devices will be demonstrated. Results of additional hypothesis testing described in Section 4.2.3 will have no effect on the success or failure of the clinical investigation.

8.6 Interim Analysis

No interim analysis will be performed during the comparative efficacy (crossover) study. Data from the comparative efficacy (crossover) study will be locked and available for analysis following completion of the final participant's Visit 6.

8.7 Subgroups of the Study Population for Data Analysis

A subgroup analysis of all primary and claims validation endpoints will be included for the Menopausal Population (see section 8.12), although this subgroup analysis will have no impact on the success or failure of the study.

8.8 Data Handling for Missing Data

Missing data will be imputed for participants in the intent-to-treat (ITT) population (see Section 8.12) who have missing data-points that affect the Primary Efficacy Hypothesis. Subjects who are missing the Day 28 VHI score will have their score imputed using a last observation carried forward approach (LOCF) within each period of the crossover study. (Note: The periods are VR101 treatment period, sham ring treatment period, and washout period.)

If a participant misses either an entire VR101 or sham ring treatment period (i.e. the participant drops out of the study during the 3-week washout period), the patient's ΔVHI score (see Section 4.2.1) will be imputed using a worst-case observation from the remainder of the study population. Specifically, if a participant completes the sham period but misses the entire VR101 study period, the lowest VR101 ΔVHI value will be assigned, and if a participant completes the VR101 study period but misses the entire sham study period, the highest sham ΔVHI value will be assigned.

8.9 Exclusion of Data

All data collected and imputed as described in Section 8.8 will be used for the testing of the Primary Efficacy Hypothesis.

8.10 Justification for Washout Period

The exact duration of benefit provided by VR101 following ring removal has not been determined using objective data (VHI scores) collected during CI01. However, in a follow-up call conducted at the end of CI01 (typically 7 days after VR101 removal), participants were asked how long the moisture provided by VR101 persisted following removal of the final VR101. The median response reported by CI01 participants was that the duration of moisture persistence was 3 days after removal of the last VR101 device, with a minimum reported persistence of effect of 2 hours, and a maximum of 7 days (7-day values were censored at 7 days; that is, this 7-day response was the maximum possible duration of effect that could be reported. 3 out of 18 participants who responded to the question on the duration of moisturizing effect after removal of the last VR101 device reported that the effect lasted 7 days). Based on the data reported, we estimate that 99% of the population would stop experiencing benefit from VR101 in 9.85 days or less, using a generalized extreme value distribution model (R 2.3.2; evd package 2.3-2).

We note that the limitations to this approach are that it is possible that the 3 patients reporting a 7-day response actually experienced benefit beyond 7 days; and the data set is small (18 participants). To account for uncertainties introduced by the small sample size and the censoring of data at 7 days, the estimated 9.85-day duration of the moisturizing effect in 99% of the population after use of the last VR101 device can be very conservatively doubled to 19.7 days. We have been even more conservative, setting the washout period to 21 days to minimize any carryover effect of treatment by the sham or VR101 in the first part of the crossover study to the crossover treatment.

8.11 Adjustment for Multiplicity

If both the primary efficacy and safety hypotheses are met, then hypotheses for Claims 1, 2, and 3 will be tested using a hierarchical testing approach in order to control for multiple testing. Claim 1 will be tested first and if the null hypothesis is rejected, then Claim 2 will be tested. If the null hypothesis for Claim 2 is rejected, then Claim 3 will be tested.

8.12 Definition of Study Populations for Analysis

THE FOLLOWING STUDY POPULATIONS HAVE BEEN DEFINED FOR THIS INVESTIGATION:

Intent-to-Treat (ITT) Primary Efficacy Hypothesis Population: All patients who meet inclusion/exclusion criteria and are randomized will be included. Any missing day 0 or day 28 VHI scores will be imputed as defined in section 8.8.

Menopausal Population: All members of the ITT population who self-report to being menopausal (have not experienced a menstrual period in the 12-month period prior to the study).

Safety Population: All VR101 devices in all study arms that are successfully inserted and used in accordance with the provided instructions for use will be included as a basis for determination of SADE proportion.

Claim 1 Population: All participants who report a daily vaginal dryness severity following their first VR101 use (Visit 2/5, depending on study arm) and report a weekly average vaginal dryness severity prior to their first VR101 insertion (Visit 1/4, depending on study arm), will be included in the analysis for Claim 1. See section 5.4.5 for relevant survey questions.

Claim 2 Population: All participants in group V1S2 who respond to the appropriate survey question (see section 5.4.6) immediately following their first VR101 insertion (Visit 1) will be included in the analysis for Claim 2.

Claim 3 Population: All daily diary responses recorded regarding VR101 comfort during use (see section 5.4.6) will be included in the analysis for Claim 3.

9 DATA COLLECTION AND MANAGEMENT

Paper CRFs (Case Report Forms) will be used for data collection during the study. Paper CRFs will be printed on 2-part NCR (no carbon required) with a copy retained by the investigators at the conclusion of the study.

Data from CRFs will be transcribed into an electronic database by the sponsor using double data-entry following study opening. Since the hand-written original CRF copies will serve as the official study record, Sponsor/analyst bias does not present concern to the study, provided double data-entry and an additional, independent data audit of database transfer is performed.

Following the final participant's Visit 6, data from the comparative efficacy (crossover) study (all data from Visits 1-5 and all data from Visit 6 except for the Post-Insertion survey) can be locked and the study blind can be broken. At this time, comparative efficacy (crossover) study data will be available for analysis.

10 AMENDMENTS TO THE CIP

Amendments to the CIP require written authorization of the Sponsor before they are recommended to the IRB(s) for approval. No changes will be made to the devices or the CIP without Sponsor and IRB approval.

To revise the CIP, the written proposed changes will be reviewed and approved by the Sponsor and submitted to the IRB for approval before any changes to the device, treatment procedures, assessment methods, data analysis, or any other procedures documented in the CIP may be made, or any additional information may be added.

11 DEVIATIONS FROM THE CIP

11.1 Acceptable Circumstances for Deviations to the CIP

Investigators shall not deviate from this CIP, except under the following circumstances:

- Deviations may be made with prior approval of the Sponsor if made in deference to participant's rights, safety and well-being, or the scientific integrity of the clinical investigation.
- Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human participants may proceed without prior approval of the Sponsor and the IRB.

Such deviations shall be documented and reported to the Sponsor and the IRB as soon as possible.

11.2 Procedure for Disqualification and Replacement of a Principal Investigator

Any PI (Principal Investigator) or Sub-PI who has been documented to consistently deviate from this CIP, and/or consistently endanger participant's rights, safety and wellbeing, or the scientific integrity of the clinical investigation, may be removed from the investigation.

12 DEVICE ACCOUNTABILITY

12.1 Access to Devices

Investigational rings (VR101 devices and sham rings) will be stored in a locked cabinet that will only be accessible by the PI and study coordinator. Only the study coordinator and designated staff members will have access to this cabinet and to the Device Accountability log, which contains the list of device numbers assigned to each subject.

12.2 Physical Location of Investigational Devices

The Sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices and shams to the investigation sites until return or disposal.

12.3 Use of Devices

Investigational devices and sham rings shall only be used in a manner specified by this CIP and the clinical protocol.

12.4 Distribution of Devices from the Sponsor to Clinical Sites

The Sponsor will deliver a specified number of VR101 and sham samples to each clinical site. Each clinical site will maintain Device Accountability Logs (see below), to which an entry must be made each time a VR101 or sham ring is given to a participant, or unused spare or used VR101 or sham ring is returned to the clinic by a participant.

12.5 Device Accountability Log

The principal investigator, study coordinator or an authorized designee shall keep a Device Accountability Log for VR101 and sham control rings which shall include:

- The date of receipt and number of devices received from the Sponsor.
- The lot number or any other unique identifier of the rings received.
- The expiration date of rings received, if applicable.
- The number and unique IDs of rings administered to each participant, along with their unique participant identifier, and the date issued.
- The number of unused rings returned by each participant, along with their unique participant identifier, device identifiers and the date.
- The number of used rings received from each participant along with their unique participant identifier, device identifiers and the date.

13 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES AND REPORTING EVENTS AND DEFICIENCIES

All Adverse Events reported by participants or observed by a clinician during the study, whether or not Device Related, must be recorded using the Adverse Event Form (Attached). All Adverse Event Forms must be provided to the Sponsor. Certain Adverse Events must be reported to the Sponsor, IRB and/or FDA as they occur throughout the study (see below and in Sections 13.7 through 13.11).

SAEs and SADEs (as defined below) are to be reported to the Sponsor and IRB within 24 hours of the PI becoming aware of their occurrence.

All ADEs (as defined below) are to be reported to the Sponsor within 5 days of their occurrence if study staff determines that they are possibly, probably or definitely related to use of an investigational device (VR101 or sham control).

13.1 Definitions

Definitions below were constructed based on guidance from and definitions provided in ISO 14155 and 21 CFR 812.3.

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to VR101 use.

Serious Adverse Event (SAE): An AE that leads to:

- Death
- A serious deterioration in the health of the participant, that resulted in any of the following:
    - A life-threatening illness or injury
    - A permanent impairment of a body structure or a body function
    - In-patient or prolonged hospitalization
    - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- Fetal distress, fetal death or a congenital abnormality or birth defect.

Adverse Device Effect (ADE): An AE related to use of VR101.

Serious Adverse Device Effect (SADE): An ADE that results in any of the consequences characteristic of a SAE.
Unanticipated Serious Adverse Device Effects (USADE): Any SADE that was not previously identified in nature, severity, or degree of incidence in this CIP or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Use Error: Act or omission of an act that results in a different response to VR101 than intended or than expected by the user.

Device Deficiency: Inadequacy of a medical device (VR101) with respect to its identity, quality, durability, reliability, safety or performance.

The following table, copied from ISO 14155:2011, summarizes how adverse events will be categorized.

Adverse event categorization

Table F.1 presents categories of adverse events.

Table F.1 — Categories of adverse events

ADVERSE EVENTS	Non-device-related	Device- or procedure-related	
Non-serious	Adverse Event (AE)[a] (3.2)	Adverse Device Effect (ADE) (3.1)	
Serious	Serious Adverse Event (SAE)[b] (3.37)	Serious Adverse Device Effect (SADE) (3.36)	
		Anticipated	Unanticipated
		Anticipated Serious Adverse Device Effect (ASADE) (3.42, Note)	Unanticipated Serious Adverse Device Effect (USADE) (3.42)

a Includes all categories.

b Includes all categories that are serious.

13.2 Anticipated Adverse Events (AE)

Following is a list of adverse events that may occur when VR101 or sham is used:

- Discomfort/pain/pressure (vaginal, abdominal)
- Vaginal/cervical tissue irritation
- Itching
- Burning
- Vaginal discharge/excess vaginal secretion
- Malodor
- Non-menstrual vaginal/cervical bleeding
- Nausea
- Coital problems
- Penis discomfort (pain, itching, irritation)
- Increased urinary urge
- Increased incontinence
- Constipation
- Bowel obstruction

13.3 Anticipated Adverse Device Effects (ADE)

Following is a list of adverse events that may be related to the use of VR101 or the sham:

- Device-related discomfort
- Device-related vaginal itching/burning/irritation

- Device-related non-menstrual bleeding
- Toxic-shock syndrome
- Ring adherence to the vaginal wall
- Inability of user to remove the ring
- Bowel obstruction
- Ring breakage that causes injury
- Device-related infection
- Device-related vaginal/cervical irritation
- Physical interference with other intravaginal or intrauterine devices

13.4 Device Deficiencies

Following is a list of device deficiencies that may be related to failure of VR101 or sham to meet its acceptance criteria:

- Outer polymeric ring is damaged - no release of contents
- Outer polymeric ring is damaged - release of contents
- Ring weld fails - no release of contents
- Ring weld fails - release of contents
- Device has rough surfaces
- Device will not stay in place
- Device is contaminated (on removal from package, extraneous matter is observed)
- Device is too rigid
- Device is too soft
- Device is too large
- Device is too small
- Device is too slippery
- Device cannot be easily inserted
- Device cannot be easily removed
- Instructions are missing and/or hard to follow
- Packaging is difficult to open

13.5 Possible Use Errors

Following are possible use errors, which do not indicate failure of VR101 or sham to meet its specifications:

- Placement of ring in the urinary tract
- Placement of ring in the anus or colon
- Oral contact with the device
- Use of damaged device
- Use of contaminated device (packaging damaged)
- Use of user-contaminated device

- Use of user- damaged device

13.6 Unanticipated Serious Adverse Events

Unanticipated Serious Adverse Events (USAEs) are adverse events occurring during the course of a clinical study that meet the following criteria:

- Serious
- Unanticipated
- Definitely, probably, or possibly related to the investigational device or sham

An unanticipated adverse event is any adverse event occurring in one or more subjects participating in a research protocol, whose nature, severity, or frequency is not consistent with either:

- The unknown or foreseeable risk of adverse events associated with the procedures involved in the research that are described in the protocol related-documents, such as the IRB-approved research protocol, and applicable investigator brochure, and the current IRB-approved informed consent document, and other relevant sources of information, such as product labeling, including instructions for use.
- The expected natural progression of any underlying disease or condition of the participant(s) experiencing the adverse event.

13.7 Adverse Event Reporting Procedures

13.7.1 Unanticipated Adverse Device Effect Reporting

The FDA's Investigational Device Exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as, "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s)).

UADEs must be reported by the clinical investigator to the Sponsor and the reviewing IRB, as described below:

- Investigators are required to submit a report of a UADE to the Sponsor and the reviewing IRB as soon as possible, but in no event later than 8 working days after the investigator first learns of the event (§ 812.150(a)(1). The FDA requirement is for reporting within 10 days, which has been reduced by 2 days to allow more time for investigation).
- Sponsor must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10

working days after the Sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1)).

- [From 21 CFR 812.46 (b)(2)]: A Sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the Sponsor makes this determination and not later than 15 working days after the Sponsor first received notice.

13.7.2 Adverse Event Reporting

Any adverse event (as identified above), whether anticipated or not, shall be reported by the investigator to the Sponsor as soon as possible, but in no case later than 5 days from the date of its occurrence.

13.8 Resumption of Terminated Studies

Since the device is a non-significant risk (NSR) device, the Sponsor is required to seek IRB approval, but not necessarily FDA approval to resume a terminated investigation. However, if the investigation was terminated under 21 CFR 812.46(b)(2) (see section 13.7.1 above), FDA and IRB approval are required to resume a terminated study.

13.9 Device Deficiency Reporting

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of an investigational device shall be documented throughout the clinical investigation and appropriately managed by the Sponsor.
Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence:

- If either suitable action had not been taken,
- If intervention had not been made, or
- If circumstances had been less fortunate, shall be documented in the Sponsor's records.

Any device deficiencies (as identified above) shall be reported by the investigator to the Sponsor as soon as possible, but in no case later than 5 days from the date of their occurrence.

13.10 Follow-Up for Adverse Events

Participants experiencing device-related adverse events will be followed by investigators at the investigation site until the clinical situation associated with the device-related adverse event is resolved, stabilizes or becomes chronic.

13.11 Communication Plan

Adverse events at any of the study sites will be brought to the PI's attention when identified. Those that are "reportable" events will be submitted to IRBs. The Sponsor will discuss any adverse events that impact the investigation with staff members at all study sites.

Any approved changes to the investigational plan will be communicated to the PI and research staff at all IRB-approved study sites. Any changes to procedures will require training to ensure that new protocol requirements are met.

14 ETHICAL CONSIDERATIONS

This study is to be conducted according to the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements.

The Investigator is responsible for ensuring that the clinical investigation is performed in accordance with the protocol, current guidelines on Good Clinical Practice, and applicable regulatory requirements. Good Clinical Practice is a standard for the design, conduct, performance monitoring, auditing, recording, analysis and reporting of clinical investigations that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of the investigation participants are protected.

A qualified clinician will make any medical decisions and decide what medical care is given (if applicable). Each individual involved in conducting the investigation should be qualified by education, training, or experience to perform his or her respective tasks. The investigation can only start at the Investigator's site after the relevant Institutional Review Board has approved the protocol, the Informed Consent Forms and other written information is provided to the participants, all study personnel have been suitably trained, and contractual arrangements identifying responsibilities are signed.

All participants will be informed that participation is voluntary and that they can cease participation at any time without giving a reason and without penalty or loss of benefits to which they are entitled. However, the Investigator should try to exclude the possibility that a participant withdraws voluntarily because of an Adverse Event.

To participate, the participant must give consent prior to enrollment in the investigation. This consent must be given in writing. The person who conducts the informed consent discussion must also sign the ICF. With consent, the participant confirms that their participation is voluntarily and that they will follow the instructions of the investigator and answer the questions asked. Signatures must be personally provided and dated.

Prior to participation in the investigation, the participant should receive a copy of the signed and dated written ICF and any other pertinent written information. The Consent form must include all elements required by law, local regulations, Good Clinical Practice and International Conference on Harmonization (ICH) guidelines, and Food and Drug Administration (FDA) requirements as well as any investigation-specific items.

Neither the Investigator, nor their staff should coerce or unduly influence a participant to participate in, or continue participating in, the investigation. Ample time must be allowed for the participant to make his or her decision to participate in an investigation and to make further enquiries about the investigation.

The original signed and dated consent form will be kept by the Investigator.

14.1 Institutional Review Board (IRB)

Institutional Review Boards safeguard the rights, safety, and well-being of investigation participants. Thus, the IRB will obtain, and document receipt of, the following documents provided by the Sponsor:

- Clinical Investigation Protocol and, if applicable, substantial amendments.
- Template Informed Consent Form and any other information that the Investigator proposes for use in the investigation.
- Participant recruitment procedures (e.g., advertisements).
- Written information to be provided to participants (if applicable).
- Investigator's Brochure.
- Safety information.
- Information about payments and compensation available to participants.

In addition, the PI will keep the following documents on file:

- Investigator's current *curriculum vitae* and/or other documentation evidencing qualifications.
- Any other documents that the IRB may need to fulfill its responsibilities.

J3 BIO (Sponsor) will request that the IRB for the site, or other regulatory authorities, where applicable, provide its written procedures and membership or voting lists. The IRB shall maintain records of its activities and minutes of its meetings. All relevant records pertaining to the investigation shall be kept for a period of at least five years after the completion of the investigation and will be made available to regulatory authorities on request.

14.2 Responsibilities

14.2.1 Principal Investigator

The Principal Investigator, in general, is the person responsible for the conduct of the investigation at an investigation center. If a team of individuals at the site conducts the investigation, the Investigator is the responsible leader of the team and will be called Principal Investigator (PI). The PI must maintain a signed list of appropriately qualified persons to whom he/she has delegated significant investigation-related duties, which must be specified. A copy is held in the site's files and the original will be sent to the Sponsor (e.g., Delegation of Authority).

14.2.2 A Sub-Investigator (Sub-I, e.g., Medical Professional, Associates)

The Sub-Investigator is any individual member of the clinical investigation team designated and supervised by the PI at an investigation site to perform critical investigation-related procedures and/or make important investigation-related decisions.

14.2.3 Sponsor

The Sponsor is an individual or organization that takes responsibility for the initiation and/or implementation of a clinical investigation. J3 BIO accepts the responsibilities of the Sponsor.

14.2.4 Monitor

Monitoring is the process of overseeing the progress of a clinical investigation, ensuring the rights and well-being of participants, and that the investigation is conducted, recorded, and reported in accordance with the protocol. Monitoring adheres to standard operating procedures, Good Clinical Practice (GCP) and applicable regulatory requirements, and ensures that the investigation data are accurate, complete and verifiable from source document collection forms.

Before the investigation starts at the investigative site, J3 BIO's appointed monitor will ensure that the investigation site has sufficient capacity and equipment to perform the investigation. At agreed upon times, the Investigators will permit the monitor to check and verify investigation documentation (source document verification), including the CRF and other information prepared for J3 BIO (e.g., logs and reports). The Investigator shall make corrections, amendments, or clarifying statements where necessary. Investigation-related medical decisions are the responsibility of a qualified clinician or medically-qualified delegate. A written report will be completed by the monitor for J3 BIO after each visit.

The Sponsor and IRB require C*urriculum Vitae* and other relevant documents confirming the qualifications of the PI and Sub-Investigators. Any previous training in the principles of Good Clinical Practice (GCP) or experience obtained from work with clinical investigations and

participant care should be described in the *Curriculum Vitae.* When personnel changes are made, the relevant documentation (e.g., Delegation of Authority) must be updated before a new member of the team may perform assigned investigation-related activities.

See Appendix A for the proposed monitoring plan for CI02 – CIP.

15 VULNERABLE POPULATIONS

The conduct of this study will not deliberately solicit participation from nor enroll participants from vulnerable populations.

16 SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

The investigation may be prematurely terminated by the Institutional Review Board, regulatory authorities, or the Sponsor, if for example, the perception of the risk to benefit ratio becomes unfavorable for the continuation of the investigation. A decision to cease the investigation in all centers is binding to all Investigators. If the investigation is prematurely terminated or suspended for any reason the Investigator shall promptly inform the participants, ensuring appropriate therapy and follow-up for all participants and informing the regulatory authorities (where appropriate) and the institution where the investigation was being performed.

17 CONFLICTS OF INTEREST

Any PI or Sub-I who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the maximum allowable by their institution) must fully disclose the nature of the conflict of interest in accordance with Sponsor policies and applicable federal, state, and local laws and regulations.

18 PUBLICATION POLICY

Neither complete nor any part of the results of the study obtained under this protocol, nor any information provided to the Investigator for the purposes of performing the study, will be published or passed on to any third party without the written consent of the Sponsor. Any Investigator involved in this study is obligated to provide the Sponsor with complete test results and all clinical data obtained from participation in this study. The results of this clinical investigation may be submitted for publication at the discretion of the Sponsor.

19 RECORDS AND REPORTS

Requirements for records and reports shall be identified in the Standard Operating Procedures (SOPs) or Good Clinical Practice (GCP) documents that identify the responsibilities of the Sponsor, Investigator, and Monitor.

20 BIBLIOGRAPHY

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21 APPENDICES

21.1 Appendix A – Proposed Monitoring Plan for Clinical Research Associate (Monitor)

Proposed Monitoring Plan for CI02: A Pivotal Clinical Investigation to Evaluate the Safety and Efficacy of J3 Bioscience Lubricating Intravaginal Ring VR101 in Relieving Symptoms of Vaginal Dryness

Due to the relative simplicity of the clinical investigation, the following minimal monitoring schedule (plan) is to be followed. Monitoring will at least occur as described below.

NOTE: Study monitors must not be aware of any participant randomization assignments (maintained by the Sponsor) at any time before the Study is opened (See Section 9).

To initiate the investigation
Investigation initiation will require monitoring to determine the adequacy of:

- Principal Investigator (PI) qualifications and/or experience (assessed by questionnaire/interview).
- Clinical investigation site capabilities (assessed by visiting the site, viewing the facility and asking questions) including adequacy of the following:
    - Qualifications and/or experience of the site team
    - Resources, including facilities, laboratories, equipment, and a qualified investigation site team
    - Access to an adequate number of subjects.

- Documentation to assure approved documents required to initiate the investigation are understood, approved and on file with the Sponsor and investigator, as appropriate, including:
    - CIP
    - IB
    - The informed consent form (ICF)
    - CRFs
    - The instructions for use
    - Any written clinical investigation agreements, as appropriate.

- Assessment of whether the sites have access to an adequate number of investigational devices.
- Assessment of whether the investigators have been trained in the use of the investigational device, and the PI is familiar with the indicated responsibilities of the PI, as described in Procedures for Selection and Qualification of Clinical Investigators GCP004 and Principle Investigator Responsibilities Agreement F-GCP-004-02.

At an interim time during the investigation, preferably after the enrollment of participant 3 and before the enrollment of participant 5, and after treatment of participant 20 and before enrollment of patient 30:

The monitor shall perform routine on-site monitoring visits to verify:

- Compliance with the CIP and any subsequent amendment(s) is maintained (**NOTE**: Deviations shall be discussed with the principal investigator(s) or authorized designee, documented and reported to the Sponsor).
- Only authorized individuals, as identified in PI records, are participating in the clinical investigation.
- The investigational device is being used according to the CIP or instructions for use and that, where modifications are required to the device, its method of use or the CIP, these are reported to the Sponsor.
- Investigation site resources, including laboratories, equipment, and the investigation site team, remain adequate throughout the duration of the clinical investigation.
- The PI continues to have access to an adequate number of participants and investigational devices.
- Signed and dated informed consent forms have been obtained from each participant at the point of enrollment or before any clinical-investigation-related procedures are performed.
- Source documents and other clinical investigation records are accurate, complete, up-to-date, stored, and maintained appropriately.
- CRFs and queries are complete, recorded in a timely manner, and consistent with source documents.
- Appropriate corrections, additions or deletions are made to the CRFs, dated, explained if necessary and initialed by the principal investigator or by his/her authorized designee; (**NOTE**: the monitor shall not make corrections, additions or deletions to the CRFs).
- All adverse events and device deficiencies are reported to the Sponsor, and all serious adverse events and device deficiencies that could have led to a serious adverse device effect are reported to the Sponsor without unjustified delay.
- All serious adverse events and deviations are reported to the EC and IRB, if required.
- The storage and investigational device accountability documents are correct and the traceability process is being followed.
- All other required reports, notifications, applications, submissions and correspondence are maintained in the investigator's files and are accurate, complete, timely, legible, dated, and identify the clinical investigation.
- Participant withdrawal has been documented (**NOTE**: The monitor shall discuss this with the principal investigator or his/her authorized designee).
- Participant non-compliance with the requirements stated in the informed consent has been documented and the monitor shall discuss this with the principal investigator or his/her authorized designee.
- The principal investigator and investigation site team are informed and knowledgeable of all relevant document updates concerning the clinical investigation.
- Any corrective and preventive actions, as needed, have been implemented and are effective.

At the conclusion of the study, preferably within one week of the last day the last participant participated in the study (not including any follow-up discussions)
The purpose of the close-out monitoring activities will be to ensure that the PI's records are complete, all documents needed for the Sponsor's files are retrieved, remaining clinical investigation materials are disposed of, previously identified issues have been resolved and all parties are notified.

Records will be reviewed to assure that:

- All essential documents are complete and up to date.
- All CRFs are completed.
- All outstanding queries are resolved.
- The current status of all ongoing adverse events is documented.
- Arrangements are made for archiving and record retention.
- Arrangements are made for documenting disposition of any:
    - Investigational devices
    - Other remaining samples (e.g., biological samples)
    - Other clinical investigation materials or supplies

- Appropriate parties are notified, including:
    - EC (IRB)
    - Clinicaltrials.gov website
    - Regulatory authorities (i.e., FDA, Notified Bodies, Authorized Representatives and Competent Authorities), as required

When a final draft of the Clinical Investigation Report is available
After close-out of the clinical investigation, a report of the clinical investigation shall be completed in accordance with the applicable regulations, even if the clinical investigation was terminated prematurely. The report shall be reviewed to assure the items below.

- The clinical investigation report is in written form.
- The clinical investigation report shall include identification of the device(s), a description of the methodology and design of the clinical investigation, any deviations from the CIP, data analysis together with any statistics and a critical appraisal of the aims of the clinical investigation.
- The clinical investigation report shall take into account the data from each investigation site and for all subjects. No participant is identifiable either from the clinical investigation report or the published results.
- Where applicable, the clinical investigation report is made available to the coordinating investigator and all principal investigators for review and comment. The Sponsor shall maintain records confirming that the clinical investigation report has been provided for review. If a reviewer does not agree with all or part of the clinical investigation report, his/her comments are recorded and communicated to the other PIs.
- Where required by national regulations, the Sponsor and coordinating investigator is asked to provide their signatures, indicating their agreement with the content of the

clinical investigation report. If no coordinating investigator is appointed, the signature of the principal investigator(s) is obtained.

- In accordance with applicable requirements, the clinical investigation report is provided to the EC(s) and regulatory authorities.

21.2 Appendix B – Participant Survey Questions Used for Validation of Claims

Claim 1: VR101 relieves vaginal dryness symptoms for up to 7 days in a majority of participants, as assessed by users.

The following question will be asked during Visit 1 and 4. The responses recorded immediately prior to insertion of the first VR101 will be used as the baseline value for validation of claim 1.

On AVERAGE, how would you rate your VAGINAL DRYNESS over the **Past 7 Days?** That would be since the last ___(day of the week)

I have not experienced vaginal dryness *Mild* *Moderate* *Severe*

The following definitions are also given prior to asking the question:

- *When we say "**mild**," we mean that any symptoms you have cause **NO or MINIMAL interference** with your usual social or functional activities.*
- *When we say "**moderate**," we mean that your symptoms cause **MORE THAN MINIMAL interference** with usual social and functional activities.*
- *When we say "**severe**," we mean that your symptoms cause an **INABILITY to perform some or all** of your usual social and functional activities.*

The following question will be asked at each visit. The responses recorded immediately following use of the first VR101 device (Visit 2 or Visit 5) will be used to assess the validity of claim 1.

Rate your vaginal dryness TODAY, that is, in the last 24 hours?

I have not experienced vaginal dryness *Mild* *Moderate* *Severe*

The following definitions are also given prior to asking the question:

- *When we say "**mild**," we mean that any symptoms you have cause **NO or MINIMAL interference** with your usual social or functional activities.*
- *When we say "**moderate**," we mean that your symptoms cause **MORE THAN MINIMAL interference** with usual social and functional activities.*
- *When we say "**severe**," we mean that your symptoms cause an **INABILITY to perform some or all** of your usual social and functional activities.*

Claim 2: VR101 is easy to use by following the provided instructions for use.

The following question will be asked as part of each post-removal questionnaire. Responses recorded following removal of the first VR101 will be used to assess the validity of Claim 2.

When responding to the next statement, consider your complete experience with the ring you are currently using, from inserting the ring last week to removing it today: The ring was easy to use by following the provided instructions. (Please check the box to the right of each statement that best describes your experience REMOVING the ring TODAY.)

Agree completely	
Agree a lot	
Agree somewhat	
Agree a little	
Neither agree nor disagree	
Disagree a little	
Disagree somewhat	
Disagree a lot	
Disagree completely	

Claim 3: VR101 is comfortable during use.

The following question will be asked as part of each daily diary.

The ring was comfortable to me today. (Please check the box to the right of each statement that best describes your experience with the ring TODAY.)

Agree completely	
Agree a lot	
Agree somewhat	
Agree a little	
Neither agree nor disagree	
Disagree a little	
Disagree somewhat	
Disagree a lot	
Disagree completely	