CI03: A Clinical Investigation to Evaluate Efficacy of the J3 Bioscience Lubricating Intravaginal Ring VR101 as a Personal Lubricant Device in Women

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SPONSOR:
J3 Bioscience, Inc. (J3 Bio, formerly named ViroPan, Inc.)
825 North 300 West, Suite N231
Salt Lake City, Utah 84103
Email: tmccabe@j3bio.com
Mobile: 801-550-9956
Office: 801-931-4756
Fax: 866-768-9341

OFFICE ADDRESS:
J3 Bioscience, Inc.
825 North 300 West, Suite N231
Salt Lake City, Utah 84103
Email: tmccabe@j3bio.com
Mobile: 801-550-9956
Office: 801-931-4756
Fax: 866-768-9341

AUTHORIZED REPRESENTATIVES (for studies conducted in the EU or elsewhere):

For studies conducted in the EU: ProMedt Consulting GmbH

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 (Pilot)
CI02	Clinical Investigation 02 (Pivotal)
CI03	Clinical Investigation 03 (Pivotal)
CHA	Clinical Hazard Assessment
CRA	Clinical Research Associate
CRF	Case Report Form
EC	Ethics Committee
FDA	Food and Drug Administration of United States
FSFI	Female Sexual Functioning Index
FSFI-LD	FSFI Lubrication Domain
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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Investigational Sites/PIs: Advanced Clinical Research/aka Velocity Clinical Research

Site 01 – West Jordan, Utah:

Principal Investigator: (Study Doctor)	**Barbara Rizzardi, MD**
Telephone:	**801-542-8190 (24 Hours)**
Address:	**Advanced Clinical Research 3590 West 9000 South Suite 300 West Jordan, UT 84088**

Site 02 – Meridian, Idaho

Principal Investigator: (Study Doctor)	**Mark Turner, MD**
Telephone:	**208-377-8653 (24 Hours)**

Address: **Advanced Clinical Research**
2950 East Magic View Drive
Meridian, ID 836452

Institutional Review Board (IRB):
IntegReview IRB
3815 S. Capital of Texas Hwy
Suite 230
Austin, Texas 78704
512-326-3001

STUDY SUMMARY

Title	**A Clinical Investigation to Evaluate Efficacy of the J3 Bioscience Lubricating Intravaginal Ring VR101 as a Personal Lubricant Device in Women**
Short Title	Efficacy of VR101 as a Personal Lubricant
Protocol Number	CI03-CIP
Phase	Pivotal
Methodology	Randomized, double-blind, sham-controlled, 4-week parallel group study
Study Duration	7 weeks (including a 2-week open-label extension and a 1-week safety follow-up)
Study Centers	Study is designed as a multi-center trial (at least 2 sites) with approximately equal enrollment
Objectives	Primary To evaluate the efficacy of VR101 as a personal lubricant 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 (as shown by the proportion of participants with FSFI-LD ≥ 4.5 following 4 consecutive weeks of weekly ring use being higher for VR101 than the sham).
Number of Participants	A minimum of 160 females (80 in each arm) will be randomized to VR101 or sham ring during the treatment phase of the study

Diagnosis and Main Inclusion Criteria	Sexually active women who report with individual question scores of between 1 and 3, inclusive, on all FSFI Lubrication Domain questions (7, 8, 9, and 10).
Study Product, Route, Regimen	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. Participants will be instructed to exchange with a new device every 7 ± 1 days.
Duration of administration	6 weeks (4-week double-blind parallel group study plus 2-week open label extension)
Reference Therapy	VR101 will be compared to a sham ring
Statistical Methodology	The primary efficacy analysis will be a superiority comparison between the proportion of participants who report FSFI-LD (lubrication domain score) scores of 4.5 or greater after using VR101 or the sham ring for 4 weeks.

1 SYNOPSIS

This Clinical Investigation (CI03) is designed to validate the efficacy of the VR101 lubricating Intravaginal Ring (IVR) as a personal lubricant device. In the proposed clinical investigation, participants will be divided into two groups for the study, VR101 device and sham ring. Participants will use VR101 devices or sham rings for 28 days in a randomized, double-blind, parallel group design.

1.1 Sample Size

Participants will be enrolled to ensure at least 160 subjects (80 in each group) are randomized to the VR101 device or sham ring group.

As this is a multi-site study, the study coordinator will monitor enrollment to ensure nominally equal representation of the 160 subjects across the sites, for example if two sites are selected, at least ~1/3 of the participants (54) will be enrolled at each site.

1.2 Investigational Devices

VR101 devices and sham rings for the clinical investigation will be manufactured by an ISO 13485-certified and/or FDA Quality System Regulation (QSR)-compliant vendor.

1.3 Summary of Endpoints (see Section 5.1.1 for details)

1.3.1 Primary Efficacy Endpoint

- Proportion of participants that experience increased vaginal lubrication that enhances ease and comfort of intimate sexual activity, defined as a FSFI-LD ≥ 4.5 following 4 consecutive weeks of weekly ring use.

1.3.2 Safety Endpoint

- All adverse events (AE) and adverse device events (ADEs) will be recorded throughout the study and will be assessed for severity and their relatedness to VR101 use.

1.3.3 Exploratory Endpoints

- Improvement in FSFI total score
- Improvement in all FSFI domains (except lubrication), which include desire, arousal, orgasm, satisfaction, and pain domains

1.4 Summary of Study Schedule and Study Schematic

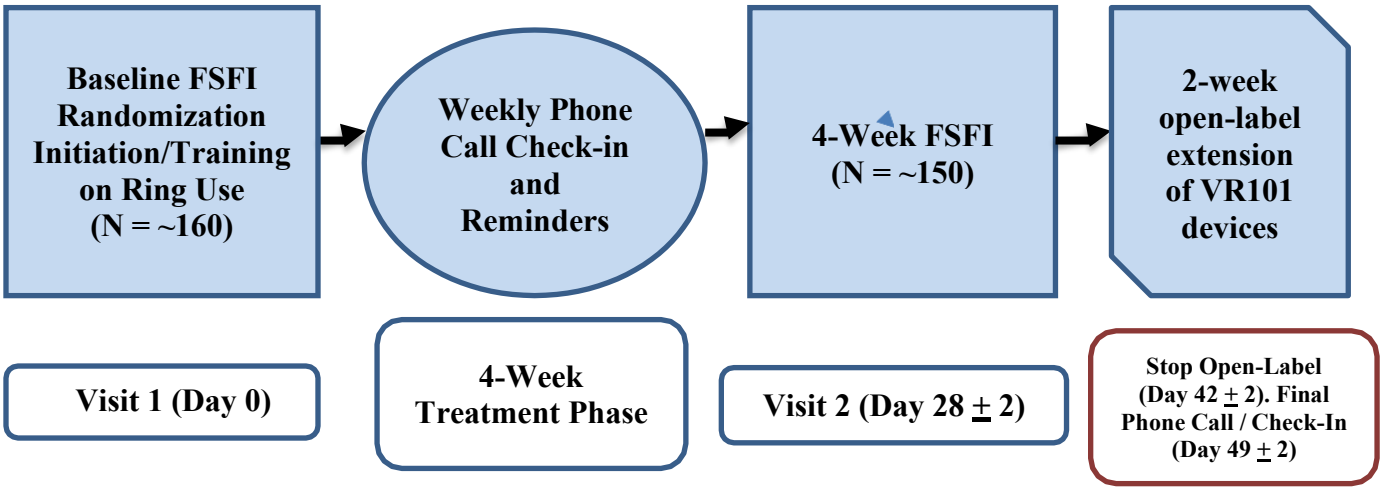

Figure 1. Study Schematic

- After a participant has read and signed the Informed Consent Document and has met all inclusion and exclusion criteria, she will be randomized into either the VR101 device or sham ring group.
- Participants will be instructed to use the randomly assigned device continuously and exchange with a new device every 7 days for the next 4 weeks.
- Study staff will complete a follow-up call with participants on the 7th, 14th, and 21st day following randomization to remind them to remove their current device and insert a new ring.
- Participants will return for a final study visit on day 28 ± 2 where the FSFI survey will be administered.
- Participants will be offered two additional VR101 devices for a 2-week open-label extension.
- A final follow-up call will occur 1 week after the end of the open-label extension.

2 BACKGROUND

2.1 Purpose

The purpose of this Clinical Investigation, internally designated CI03, is to evaluate efficacy of the J3 Bioscience, Inc. (J3 Bio) lubricating intravaginal ring, VR101, as a personal lubricant device in women. After reviewing 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," and in CI02, "A Pivotal Clinical Investigation to Evaluate the

Safety and Efficacy of J3 Bio Lubricating Intravaginal Ring (VR101) in Relieving Symptoms of Vaginal Dryness," FDA and J3 Bio agreed that VR101 safety had been successfully demonstrated.

CI03 is designed to further evaluate VR101 efficacy and will enable continued monitoring of VR101 safety. The combined safety and efficacy data from CI01, CI02, and CI03 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.

2.2 Scope

This procedure applies to the clinical investigation of VR101, Lubricating Intravaginal Ring manufactured by J3 Bio, to establish the efficacy of VR101 as a personal lubricant device and its substantially equivalent safety and efficacy to the predicate device, Replens® Long-lasting Vaginal Moisturizer in Pre-filled Applicators (Replens). 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 Design History File and/or Technical File, as appropriate.

2.3 Summary of VR101 Bench Testing

2.3.1 Bench Tests/Stability

The following characteristics of VR101 devices have been evaluated and found to be within specifications or required ranges for up to 54 months (real-time equivalent):

- Visual appearance
- Dimensions
- Mechanical force required to compress VR101
- Tensile strength
- *In vitro* release of glycerol

Condom compatibility also was evaluated and found to be acceptable per ASTM D7661-10.

2.3.2 Biocompatibility Tests

The biocompatibility of VR101 has been evaluated per ISO 10993. Results of all tests performed either on the VR101 test articles or VR101 components, as appropriate, were acceptable, indicating 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 (also sold as 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.

Based on the results obtained in the ISO 10993 and FDA-recommended studies, J3 Bio concludes that the biological and toxicological risks associated with the use of VR101 are low and acceptable, justifying the continued use of VR101 in a clinical investigation.

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 Clinical Studies

Two clinical investigations have been performed on VR101 to-date and are summarized in Table 1 and Sections 2.4.1 and 2.4.2.

TABLE 1 SUMMARY OF COMPLETED VR101 CLINICAL TRIALS

Study	Subjects Enrolled	Design	Regimen	Objective(s)	Diagnosis / Key Eligibility Criteria	Primary Endpoints/Outcomes
CI01 - Pilot	21	Open-Label	VR101, 2 devices used consecutively for 7 days each (14 days total)	Obtain preliminary data on the ability of the VR101 to relieve the symptoms of vaginal dryness in post- and perimenopausal women.	Women over the age of 40 Self-reported peri- or post-menopausal women with self-reported vaginal dryness	Statistical improvement in modified VHI (without pH) on day 3 and day 14 90% reduction in vaginal dryness frequency after 2 weeks of use No serious adverse events in study population

Study	Subjects Enrolled	Design	Regimen	Objective(s)	Diagnosis / Key Eligibility Criteria	Primary Endpoints/Outcomes
CI02 – Efficacy	72	Randomized, Double-Blind Crossover, Sham-Controlled	VR101 and sham ring, 4 devices used consecutively for 7 days each (28 days total)	To demonstrate the efficacy of VR101 in treating the symptoms of vaginal dryness To validate potential labeling claims regarding VR101 use: 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. To demonstrate that VR101 may be used by following the provided instructions, justifying its over-the-counter (OTC) use. To further the scientific/technical understanding of VR101 by surveying user's experiences	Women over the age of 35 who self-reported having experienced vaginal dryness symptoms that interfered with daily activities, including but not limited to sexual activity, in the last 60 days; and whose clinician-assigned baseline Vaginal Health Index (VHI) score was 22 or lower.	Primary efficacy endpoint (superior VHI improvement vs sham after 28 days of use) not met, but efficacy suggested through post-hoc analyses
CI02 – Long-Term Safety	57	Open-Label	VR101, 13 devices* used consecutively, each for 7 days (91 days total)	To assess the safety of VR101 when used to treat the symptoms of vaginal dryness.		No serious adverse events in 890 VR101 insertions
*Total, in one study group this included the 4 devices used in the crossover portion of CI02.						

2.4.1 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. 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.

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 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. Once participants started using VR101, the reported frequency of vaginal dryness symptoms decreased from 4 days per week 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 (all $p < 0.005$, one-tailed, normally approximated Wilcoxon signed-rank test).

Regarding safety, no serious safety concerns or adverse events were noted or reported by the participants or clinical study staff. Moreover, all 21 participants that enrolled successfully completed the study, including follow-up.

2.4.2 Summary of VR101 Pivotal Investigation (CI02)

CI02 was designed to evaluate the safety and efficacy of VR101 and establish its substantial equivalence to the predicate device, Replens® Long-lasting Vaginal Moisturizer in Pre-filled Applicators (Replens). In total, 72 women were enrolled in CI02 who self-reported experiencing vaginal dryness symptoms within the past 60 days that interfered with daily activities.

Participants were randomized upon enrollment to one of two crossover groups and were instructed to use either four each VR101 lubricating devices or four each sham rings consecutively, each for 7 days and a total of 28 days. After a 3-week washout period, participants then crossed over to use of their respective alternate device (sham ring or VR101 device) and were again instructed to use four rings or devices consecutively for 7 days each (28 days total use). Participants were then asked to continue use of VR101 for at least 13 consecutive weeks to assess VR101 safety during long-term, repeated, continuous use. Participants who finished the crossover period using VR101 last were asked to continue VR101 use for an additional 9 weeks (13 weeks total), while participants who finished using the sham ring last were switched back to VR101 use for 13 additional weeks (17 weeks total, 13 of them consecutive).

Of 890 each VR101 devices used in CI02, no SADEs were observed during the investigation, nor have any been recorded with use of VR101 to date.

Efficacy primarily was assessed using the composite Vaginal Health Index (VHI), previously published by Bachmann *et al.* (1991 and 1992). During the double-blind crossover portion of

CI02, VR101 improved composite Vaginal Health Index scores, when used for 28 days over baseline scores (Change in VHI (ΔVHI) = +1.76 ± 3.32, $p < 0.0001$, paired *t*-test vs baseline, N = 66). However, missing data in CI02 greatly contributed to a failure to meet the primary efficacy endpoint under the original statistical analysis plan.

In 5 total *post hoc* mixed model analyses, the *p*-values calculated in assessment of the primary efficacy endpoint were similar and concluded a significant difference in 28-day VHI treatment effect between use of VR101 and the sham ring ($0.01 \leq p \leq 0.02$).

The following patient-reported endpoints were also assessed to provide additional assessments of efficacy and usability and to substantiate labeling claims:

- Participants reported a significantly lower vaginal dryness severity during the final 24 hours of their first VR101 use when compared to the 7 days prior to ring use ($p < 0.0001$, paired *t*-test).
- Ninety-three percent (93%) of participants reported that VR101 was easy to use by following the provided instructions when using their first VR101 device.
- When queried in daily diaries if VR101 was comfortable during use, participants responded favorably 88% of the time.

3 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

3.1 Summary Description of VR101

VR101 is a clear, flexible, torus-shaped lubricating intravaginal ring (IVR); see Figure 2, Device Image, and Figure 3, 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.

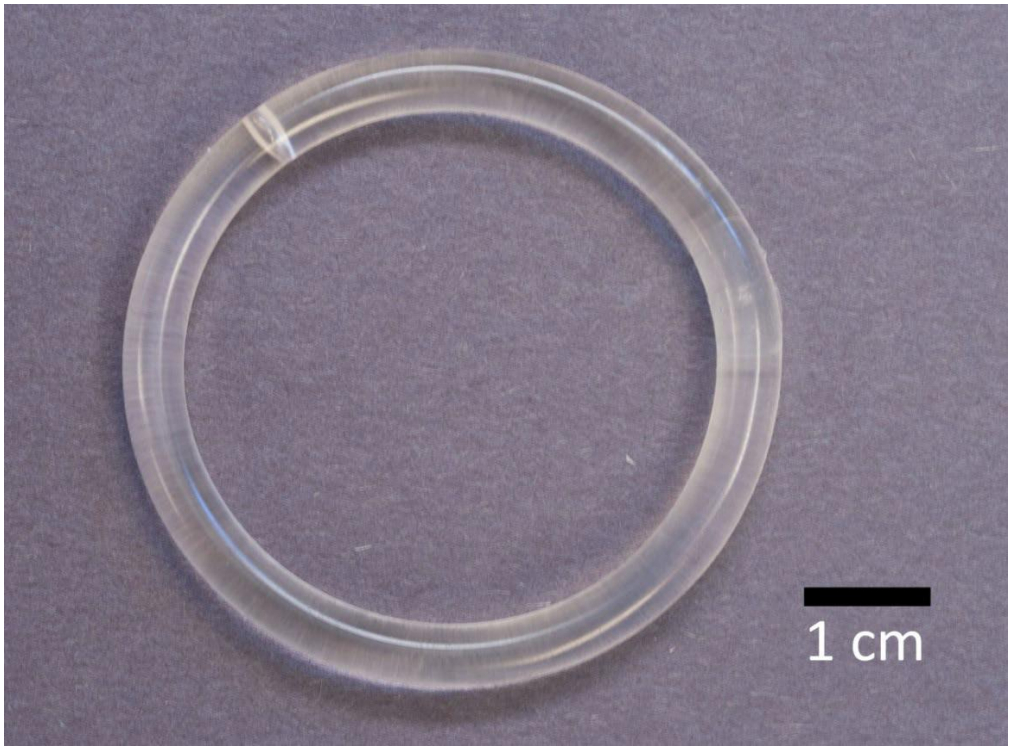

Figure 2. Top View of VR101

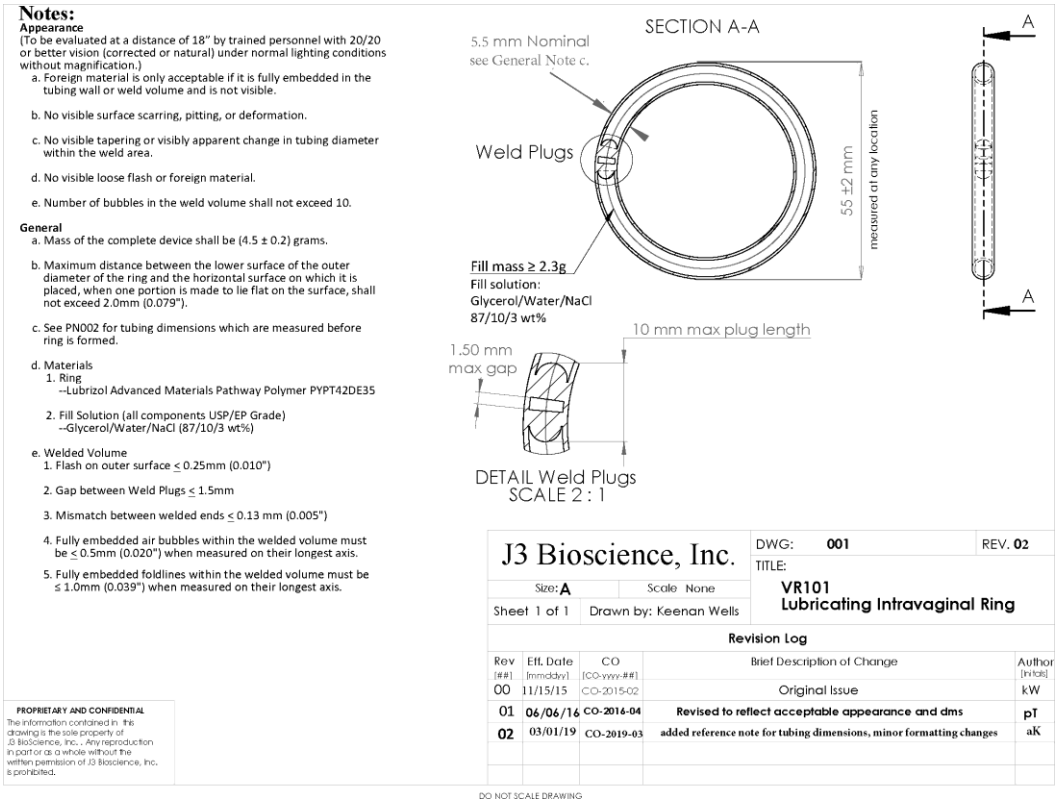

Figure 3. VR101 Manufacturing Drawing with Specifications

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 2 lists the dimensions of VR101.

Table 2. Nominal Dimensions of VR101	
Ring Characteristic	**Dimension**
Outer Diameter (ring)	55 mm
Cross-Sectional Diameter (tubing)	5.50 mm
Wall thickness (tubing)	0.65 mm

Table 3 identifies composition and weight of VR101.

Table 3: 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 4 provides the specifications for VR101 constituents. VR101 does not contain any drugs or active pharmaceutical ingredients (APIs).

Table 4. 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 VR101, 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 4. 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 VR101 Intended Use

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.

3.4 Lubricating Agent

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 two clinical investigations in women. See Sections 2.3.3 and 2.4 above for summaries of the preclinical and pilot clinical studies, respectively.

3.5 Supplier of VR101 Devices and Sham Rings

VR101 devices and sham rings manufactured by an ISO 13485-certified and/or FDA Quality System Regulation (QSR)-compliant vendor and will supply the products for the clinical investigation.

3.6 VR101 Identification

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

3.7 VR101 Lot Traceability

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

3.8 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 VR101 ring.

VR101 is intended to be available as an over-the-counter (OTC) product that will not require healthcare professional assistance or supervision for use. 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 based on reading the provided instructions for use (IFU) and labeling. All applicable warnings, precautions and contraindications are listed on the IFU.

3.9 Sham Rings

To demonstrate that efficacy results from this study are clinically meaningful, lubricating/moisturizing effects not directly resulting from VR101 must be adequately controlled. Therefore, performance of VR101 will be compared that of a sham ring.

Sham rings will be manufactured identically to VR101, except:

- Tubing will be manufactured with Biomerics Quadraflex ALE-91A, an inert (non-hydrophilic) aliphatic polyether urethane. ALE-91A has identical manufacturer-reported flexural modulus (per ASTM D790) to Tecophilic HP-60D-35 (Pathway PY-PT42DE45), is non-hemolytic (per ASTM D756), is non-cytotoxic (per ISO 10993-5), and has been used to manufacture FDA-approved, long-term (>30 day) implantable medical devices.
- No lubricating solution will be added to the device lumen or the device package.

4 OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

4.1 Study Objectives (ECH E3; 8.)

4.1.1 Primary Objectives of the Clinical Investigation

To evaluate the efficacy of VR101 as a personal lubricant for vaginal application, intended to increase vaginal lubrication and enhance the ease and comfort of intimate sexual activity.

4.2 Hypothesis of the Clinical Investigation

4.2.1 Primary Efficacy Hypothesis

Compared to the sham device, a significantly greater proportion of participants who use VR101 for 4 consecutive weeks will experience increased vaginal lubrication that enhances ease and comfort of intimate sexual activity as assessed by the Lubrication domain of the FSFI (FSFI-LD $\geq$ 4.5).

4.3 Label Claims to be Assessed in the Clinical Investigation

Successful confirmation of the Primary Efficacy Hypothesis will also validate the following proposed VR101 Label Claims:

- Use one ring every 7 days to provide lubrication during sexual activity or intercourse
- Use one ring every 7 days to reduce discomfort during sexual activity or intercourse
- Use one ring every 7 days for increased comfort and lubrication
- Helps replenish vaginal lubrication when used once every 7 days
- Provides vaginal lubrication when used once every 7 days

5 STUDY DESIGN

5.1 General Description of the Clinical Investigation (ICH E3; 9)

Clinical Phase: Pivotal

Sample Size: At least 160 participants will be randomized (1:1 ratio) into two groups to use either VR101 or the sham ring.

Study Population: Sexually active women who report experiencing lack of lubrication during intercourse, give consent to participate and meet all inclusion/exclusion criteria.

Study Type: Multi-center, double-blind, sham-controlled parallel group study (followed by optional open-label extension).

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

Study Regimen: Participants will be randomly assigned to receive either VR101 or the sham ring. Participants will then use 4 devices consecutively for 7 days each, (28 days total). Participants will be allowed to use VR101 for 2 weeks following the double-blind study in an open-label extension.

5.1.1 Study Endpoints (ICH E9; 2.2.2)

- **Primary:** Proportion of participants that experience increased vaginal lubrication that enhances ease and comfort of intimate sexual activity, defined as an FSFI-LD ≥ 4.5 with 4 consecutive weeks of weekly ring use.

- **Exploratory:** Improvement in the Female Sexual Function Index (FSFI) total composite score (Rosen 2000) and its domains (Desire, Arousal, Lubrication, Orgasm, Satisfaction and Pain) during 28 days of use.

- **Safety endpoints monitored**:
    - Any adverse events and adverse device effects (ADE)

5.1.2 Measures to Minimize Bias

- Participants will not have access to their previous responses, and thus, in any given FSFI survey participants will be unable to directly reference their previous responses.
- All participants, regardless of randomization status, will be presented with the same study materials, including device packaging and labeling, will undergo the same measurements, and will be presented with the same survey questions.

5.1.3 Test Equipment, Maintenance, and Calibration

No test equipment is needed for evaluation of safety or efficacy of device use.

5.2 Exposure to VR101 and the Sham Ring

Participants will use VR101 for up to 42 (±2) days or the sham ring for up to 28 (±2) days.

5.3 Study Participants

5.3.1 Inclusion Criteria for Participant Selection (ICH E3; 9.3 ICH E9; 2.2.1)

Clinical Investigation Participants Must:

1. Completely understand and sign the informed consent form (ability to read and understand the consent form in the English language).
2. Be at least 21 years of age.
3. Express willingness to comply with the entire study visit schedule (see Table 7 in study procedures section).
4. Over the course of the study:
    a. Abstain from the use of any vaginal moisturizers or lubricants or any other topically applied vaginal products not provided by study staff during the entirety of study participation
    b. Abstain from using lubricated or spermicide-containing male or female condoms
    c. Abstain from vaginal intercourse with a male partner using a lubricated condom

d. Abstain from any oral sex during or prior to vaginal intercourse with a male partner.
e. Must not initiate, modify or discontinue a regimen of HRT (hormone replacement therapy) or estrogen-containing birth control.

   NOTE: women who have been using non-vaginal HRT or estrogen-containing birth control (e.g., oral, transdermal) on a regular dosing interval continuously for at least 3 months may continue on the same regimen during the study

f. Abstain from use of any other vaginally-placed devices (e.g. ring, diaphragm, cervical cap, pessary products)
g. If able to get pregnant, use an approved method of contraception (per remainder of I/E criteria) to reduce their risk of becoming pregnant during the study.

5. In the previous 3 months, have had or attempted sexual intercourse with a male partner a minimum of twice per month (on average).
6. Respond to all 4 individual FSFI Lubrication Questions (7 - 10) with a score of 1, 2, or 3.
7. Attempt sexual intercourse at least 4 times during the 4-week double-blind study.

5.3.2 Exclusion criteria for participant selection

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

1. Current use of HRT (Hormone Replacement Therapy) or any estrogen-containing birth control products, unless not applied vaginally and the participant has been on a regular dosing interval for at least 3 months prior and is willing to continue the same regimen without modification throughout study participation.
2. Vulvar or vaginal procedures (biopsies, radiation) in the last 3 months.
3. Active vulvar or vaginal infections/lesions or complaints, as well as undiagnosed abnormal genital bleeding.
4. History of chronic pelvic pain, interstitial cystitis, vulvar vestibulitis, pelvic inflammatory disease within the past 3 months.
5. Known current cervical or vaginal infection.
6. Participants who have given birth or terminated pregnancy in the past 6 weeks.
7. Postpartum or post-abortion endometritis, unless symptoms resolved at least 3 months prior to study entry.
8. Current persistent, abnormal vaginal bleeding.
9. History of inability to place a vaginal ring.
10. History of any abnormality of the vagina resulting in distortion of the vaginal canal or incompatibility with vaginal ring placement.

11. Body habitus or history of lower genital tract abnormalities or prior surgeries, which may not allow the vagina to be appropriately accessed.
12. Known or suspected allergy or hypersensitivity to polyurethanes or glycerol.
13. Known current alcohol or illicit drug abuse.
14. Participants who have not recovered from adverse events due to chemotherapy or radiation treatment for cancer.
15. 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.
16. 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.
17. Current use of a vaginally-placed device (e.g. ring, pessary, cervical cap or diaphragm) unless willingness to discontinue for the study duration is expressed.
18. Pregnancy or plans to become pregnant in the next 6 months.
19. Current breastfeeding.
20. Participation in a previous ViroPan or J3 Bioscience clinical trial for VR101 (i.e. CI01, CI02)

NOTE: IUD (Intrauterine Device) 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 but are not automatically excluded from the study.

5.3.3 Points of Enrollment

Participants will be considered to be enrolled upon providing consent, meeting all inclusion/exclusion criteria and signing the Informed Consent Form.

5.3.4 Duration of Participation

Participants will be enrolled in the study for a total of up to 49 days. The study will consist of a 28-day randomized trial where participants will use either VR101 or the sham ring followed by a 14-day open-label portion and a follow-up phone call 7 days after the open-label portion.

5.3.5 Randomization and Blinding

Each enrolled subject randomly assigned in a 1:1 ratio to receive either VR101 devices or sham rings. A randomization schedule (separate for each site) will be prepared for treatment group assignment of each subject. The subject's randomization number will be

unique. This number is not the same as the subject identification (ID) number which is assigned at the time of informed consent.
The subject ID number identifies the subject and consists of the site number plus subject number for that site. The randomization number identifies the treatment; the randomization schedule provides the correspondence between the subject ID number and the randomized treatment identification (VR101 or sham).

The trial will be double-blind, meaning the subject and Investigator/staff will not have access to or knowledge of the subject's treatment assignment. Further, since the Sponsor will create and securely maintain the randomization schedules, the Sponsor and Sponsor's representatives will not be made aware of a given subject's randomization number until the blind is broken. The Sponsor will ensure that the Study Monitor does not ever have access to the randomization assignments.

As this is a multi-site study, the study coordinator will monitor enrollment to ensure nominally equal representation of the 160 subjects across the sites, for example if two sites are selected, at least 1/3 of participants (53) would be enrolled at each site. Additionally, the Sponsor will create and securely maintain a separate randomization schedule for each site to ensure appropriate site representation in the study groups.

5.3.6 Participant Withdrawal / Discontinuation

Participants may voluntarily withdraw from the investigation for any reason at any time. However, every effort will be made to schedule an Early Termination visit and collect final outcome measures as well as ascertain the reason for withdrawal.

Participants who withdraw from the study (or are removed by an investigator) due to an Adverse Event will be followed as described in Section 13.10.

Participants who begin a menstrual period during ring use should discontinue ring use and insert a new ring within 24 hours of cessation of menstruation. When a new ring is inserted, ring exchange will still occur on scheduled days (see Section 5.4.3). For example: If the new ring is inserted on day 6, 13, or 20, she will not need to change again on day 7, 14 or 21 (respectively) because leaving the ring in will still comply with the margin of error in the Visit Schedule.

Participants who become pregnant during the study will be instructed to discontinue use of study product and will be dropped from the study. Study staff will refer any such participants to a clinical facility for follow-up.

5.3.7 Number of Participants

Enrollment will continue until at least 160 participants have been randomized into the study. For a 2-site study, at least 53 (~1/3 of total) participants must be enrolled at each study site.

5.3.8 Estimated Time Needed to Enroll Participants

Based on previous studies, we anticipate that enrollment of 160 participants can be completed in approximately 2 months.

5.3.9 Total Study Duration

The clinical investigation is expected to last approximately 3 to 4 months.

5.3.10 Procedures for the Replacement of Participants

Participants will not be replaced. Data from all randomized participants will be reviewed prior to data lock. Analysis groups and methods for dealing with any missing data will be assigned prior to unblinding for the primary and secondary efficacy analyses. Refer to the Draft Statistical Analysis Plan (SAP) for further details. The SAP for this study will be finalized and approved prior to final data analysis.

5.4 Procedures

5.4.1 Participant Screening

Participants will be screened according to study site procedures.

5.4.2 Participant Enrollment / Recruitment

- Interested women will be invited to learn more about this study. 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 basic inclusion/exclusion criteria. 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.

5.4.3 Visit Schedule and Description: Frequency and Timing of Study Variables (ICH E3; 9.5.1. ICH E9; 2.2.2)

Participants must return to the clinic for determination to return unused study product and take a final FSFI survey per the schedule shown in Table 7. At that time, all participants will be given the opportunity to use active VR101 rings for a 2-week period.

Table 7. Schedule of Events

	Baseline	Treatment				Discontinuation/ Follow-Up	
Visit	**1**	**PC**	**PC**	**PC**	**2**	**Early Term*** **	**Final PC**
Day (Nominal)	0	7±1	14±1	21±1	28±2	Study Withdrawal	49±2 (35±2)*
Informed Consent	X						
Assign Subject Number	X						
I/E Criteria	X						
Demographics	X						
Height & Weight	X						
Concomitant Therapy	X				X	X	
Pregnancy Test	X				X	X	
Administer Non-Lubricated Condoms (if needed)	X						
Brief Medical History	X						
FSFI Survey	X				X	X	
Intercourse / Lubricant Use Survey		X	X	X	X	X	
Dispensing of Randomized Product / Insertion of 1st Ring in Clinic	X						
Removal of Final Randomized Ring / Dispensing of Open-Label Product Insertion of 1st Ring in Clinic					X**		
Adverse Events	X	X	X	X	X	X	X
Ring Use Log	X	X	X	X	X	X	X**
Ring Change Reminder		X	X	X			
Returned Ring Collection					X	X	

*If a participant does not elect to participate in the open-label extension, the follow-up will occur on day 35±2 instead of day 49±2.
**Only if the participant elects to participate in the open-label extension
***Only if a participant decides to withdraw participation before reaching Day 26

Visit 1 – Study Start / Randomization (Day 0)

1. Assign a Subject Number to the prospective participant and complete initial screening procedures.
2. Participants will be administered the FSFI survey (see Section 5.4.6) by a trained member of the study staff. Complete this as early as possible in the Visit, e.g., as soon as consent is obtained.
3. A staff member will conduct a Concomitant Therapy assessment, during which they will assess and record if any hormonal therapies are currently being used or have been used in the past 3 months (these may or may not disqualify the participant from enrollment, refer to Inclusion / Exclusion Criteria above). During this assessment, women still able to get pregnant will be asked about their current birth control method. If the method is allowed by inclusion / exclusion criteria (see above), they will be instructed to continue their same method. If no birth control is currently used, or their preferred method is to use condoms, they will be offered non-lubricated condoms as to allow them to participate in the study.
4. As part of the demographic assessment, participants will be queried as to their menopausal status. If a prospective participant is still able to get pregnant, she will be asked to provide a urine sample for a pregnancy test.
5. If participant meets all inclusion and exclusion criteria, they will be enrolled and given a numbered package of randomized study product. All packages will be identical in appearance and will contain 6 individually packaged study devices (either VR101 or sham ring). All packages will contain a unique number, which will be recorded by study staff.
6. Enrolled participants will be shown to a private clinic area or restroom to self-insert one of the devices from the package. Participants will be asked to insert one of these rings per the instructions for use and without clinician input. If a participant has difficulty with placement, she can ask for further instruction or choose to not place the ring and will be withdrawn from the study (this will be recorded on an Early Termination CRF and reported to the Sponsor). If the ring was successfully placed, the participant will be instructed to leave the first ring in the vagina for 7 days.

NOTE: Used rings / packaging are not intended to be collected by study staff. However, the site Study Coordinator may consult the Sponsor to determine if used devices / packaging should be collected in case of any unusual patient reports / adverse events.

7. Study staff will record the date and time that the ring was successfully placed and note any assistance needed from study staff (e.g., physical, verbal) so that it can be recorded in the Ring Use Log (Section 5.4.8).
8. Participants will be instructed to exchange with a fresh ring on day 7, day 14 and day 21.

NOTE: If the ring is expelled (unless on a normal exchange day), 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, or if the ring has been out for more than 24 hours, she will be asked to store it, if possible, in a provided re-sealable bag and bring it to her next clinic visit. If this occurs:

- If expelled After the ring had been inserted for at least 6 days: she will be asked to start her next scheduled ring a day early.
- If the ring had only been inserted for 5 days or less: she will be asked to insert a new ring, which will be removed on the next scheduled day (e.g., day 7, 14, 21 or 28).

Visit 2 – Final visit, Treatment week 4 (Day 28 ± 2)

1. Participants will be asked to report any Adverse Events (AEs), and whether or not they feel the events were related to use of the investigational device. AEs will be recorded on the Adverse Event Form. Refer to Section 13 for further detail on classification of AEs and adverse device effects (ADEs).
2. If a participant is still able to get pregnant, she will be asked to provide a urine sample for a pregnancy test.
3. Participants will be administered the FSFI survey (see Section 5.4.6) by a trained member of the study staff.
4. A staff member will conduct a Concomitant Therapy assessment, during which they will determine the participant used any unapproved medication (e.g. change of dosing frequency of HRT / hormonal birth control).
5. Following the FSFI Survey, participants will be given the Intercourse / Lubricant Use Survey (see Section 5.4.7) to assess frequency of intercourse and assess if any unapproved lubrication sources were used.
6. Participants will be again queried as necessary to complete the Ring Use Log (see Section 5.4.8) up to all events that occur during Visit 2. If the participant does not continue in the open-label extension, then all information needed to fully complete all fields of her Ring Use Log should be collected during Visit 2.
7. Participants will be asked to return any unused devices to study staff.
8. A member of the study staff will ensure that all study devices are accounted for, i.e., that the number of unused devices returned is reconciled with reported ring use.
9. The participant will then be asked if she would like to participate in an open-label extension where she can use VR101 for 2 weeks (two devices, 1 week per device). Each participant will be instructed to discontinue use her final VR101 device at day 42 ± 2 and told she will receive a final follow-up call on day 49 ± 2.
10. If the participant would like to continue, a member of the study staff will provide her with two VR101 devices. Participants will be again shown to a private clinic area or restroom to remove her device and (if she has elected to continue) self-

insert one of the devices from the package. Participants will be asked to insert one of these rings per the instructions for use and without clinician input. However, the participant may elect to take the rings with her and insert later at her convenience. The participant should dispose of her used ring in the restroom wastebasket, used rings are not intended to be collected by study staff.

Early Termination Visit

1. If a participant withdraws consent during the study (before Day 26, attempt to schedule a Visit for the participant to return study products and disclose any Adverse Events or concomitant therapy changes. Refer to Section 13 for further detail on classification of AEs and adverse device effects (ADEs).
2. During this Visit, if appropriate, participants will be asked to provide a urine sample for a pregnancy test.
3. If consent has not been withdrawn prior to the Study Visit, participants will be administered the FSFI study, Intercourse / Lubricant Use Study, and queried as needed to complete the Ring Use survey (in that order).
4. The participant will be queried regarding the reason for her withdrawal and the response will be recorded on the Early Termination CRF, record as much detail as possible (e.g. lack of lubrication, too much lubrication, difficulty place/remove a ring, adverse event (related or unrelated to device), etc.)

5.4.4 Interim Follow-Up Call Schedule

Each participant will be contacted by phone on days 7, 14, and 21 to assess their medical condition and to complete the Intercourse / Lubricant Use Survey. Participants will also be reminded to remove their current ring and replace with a fresh ring if they have not already done so. The study staff member administering the call will also query the participant to determine the date and time all ring exchanges (scheduled and un-scheduled) and temporary removals re-insertions, and if any assistance was required for insertion/removal for any of these exchanges/temporary removals.

5.4.5 Terminal Follow-Up Procedure

One (1) week after the last ring is removed, each participant will be contacted to assess her medical condition and to complete a brief 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 ring. If the participant participated in the two-week open-label extension, study staff will query the participant to complete the ring use log (see Section 5.4.8). If a participant is terminated early and returns to the clinic for a final visit (see above), all information and rings can be collected during this visit and an additional follow-up call is not needed.

5.4.6 FSFI (Female Sexual Function Index) Survey

During both study visits (and an Early Termination Visit, if applicable), each participant will be given the FSFI Survey (see Appendix A).

5.4.7 Intercourse / Lubricant Use Survey

During Day 7, 14 and 21 Phone Calls and Visit 2, participants will be given a survey to assess:

- Frequency of Intercourse since last Visit/Call
- Any uses of unapproved lubricants/sources of lubrication since the last Visit/Call

5.4.8 Ring Use Log

Study staff shall complete a Ring Use log which details the date and time of all ring insertions and removals (scheduled and unscheduled, including temporary insertions and removals) by querying participants during each Visit and Phone Call. This log should also note any time that assistance was required to place or remove a ring, and record as much detail as possible regarding the nature of these events.

NOTE: If a participant does not complete the 2 week open-label extension, study staff does not need to collect any information for the Log because no rings will have been used since Visit 2.

5.4.9 Factors That May Influence the Outcome of the Investigation

Study Compliance

If participants do not adhere to the indicated schedules (i.e., device use, surveys, study 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 and device exchange schedule. The treatment of incomplete data sets is addressed in the Statistical Analysis Plan (SAP).

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., supplementary lubrication). Participants will be queried in a repeated survey throughout the study as to whether they used any unapproved lubrication. A Concomitant Therapy assessment will be conducted at each Visit to determine if any disqualifying HRT or hormonal birth control products (see Inclusion/Exclusion criteria) were used prior to or during the study.

5.5 Monitoring Plan

The investigation will be monitored in accordance with the principles of Good Clinical Practice (GCP)." The monitoring schedule is as follows below.

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 [5-10%] participants have enrolled in the study at each site (see Monitoring Plan), and again after [30-40%] participants have enrolled at each site, and after [30-40%] participants have completed the study at each site. An additional monitoring visit will be conducted after the last participant at each site has completed the 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.

5.6 Labeling

VR101 device labeling is provided in Appendix B. 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 a 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 may distribute the bags containing the VR101 packaged devices in sealed pouches to study participants.

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 rings will be given to participants following enrollment and administration of the initial FSFI survey. Only the Sponsor or his or her authorized representative will have knowledge of which packaging identifiers correspond to either VR101 or the sham ring. The identity of administered rings will not be disclosed to any clinical staff prior to unblinding.

After turning in their unused devices (which may be VR101 devices or sham rings), participants who elect to continue in the on-label extension will be provided with a new, labeled zip-lock bag (as described above) containing two VR101 devices.

6 JUSTIFICATION FOR THE CLINICAL INVESTIGATION

6.1 Need for the Proposed Clinical Investigation

Following review of the CI02 Clinical Investigation Report, FDA requested that additional data be provided to demonstrate the clinical performance of VR101.

6.2 Safety of VR101 in Prior Studies

As described in Sections 2.4 and 2.5, two prior Clinical Investigations have been performed on VR101, where a total of 933 VR101 devices were used. No serious adverse device effects (SADEs) occurred in either clinical investigation (CI01 and CI02) study.

6.3 Justification of Study Endpoints

6.3.1 FSFI-LD

As a personal lubricant device, VR101 is intended to supplement the body's natural lubrication to enhance the ease and comfort of intimate sexual activity. The Female Sexual Function Index (FSFI) is a survey validated to assess sexual function in women. The FSFI contains 19 questions, divided in to 6 characteristic domains: Desire, Arousal, Lubrication, Orgasm, Satisfaction, and Pain. Although all of these characteristics may be improved by use of a personal lubricant, only the Lubrication domain is directly relevant to a lubricant's intended use.

J3 Bio was asked by FDA to assess VR101 efficacy through analysis of individual improvement, rather than a comparison of group mean scores. Thus, we have proposed a threshold above which a participant's LD will be deemed resolved to a clinically meaningful degree and the participant considered to be a study "responder" (LD 4.5 out of 6). In the FSFI cross-validation study (Wiegel 2005) a lubrication sub score threshold of 4.35 out of 6 was noted as an accurate discriminant of overall sexual dysfunction. Since 4.5 is the next highest achievable score above 4.35, the primary efficacy hypothesis will be supported if the proportion of participants reaching a score of 4.5 or better following 4 weeks of VR101 use exceeds that following 4 weeks of sham ring use. Participants will only be enrolled in the study if they score 1, 2 or 3 (out of 5) on all 4 Lubrication Questions at baseline. The lower bound of 1 is justified because a score of 0 on any question would indicate that the prospective participant had not attempted intercourse in the past 3 months, which contradicts one of the key study inclusion criteria. For this study to yield reliable results, only participants that demonstrate a willingness to attempt intercourse should be enrolled. The upper bound of 3 is justified because a score of 3 or less represents a non-satisfactory response to each question as follows:

- Q7 and Q9: Lubrication "about half the time" or less during intercourse.

- Q8 and Q10: Difficult, very difficult or extremely difficult to become/stay lubricated during intercourse.

6.3.2 Adverse Events / Adverse Device Effects

As in CI02, clinical staff will monitor and report all AEs throughout CI03 and attempt to determine their relatedness to VR101 use. This will continue to ensure the VR101 functions safely as a personal lubricant device. Refer to Section 13 for classification of AEs and ADEs.

7 RISKS AND BENEFITS OF VR101 AND CI03

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 has been performed and is included as Appendix C.

7.3 Risk-Benefit Ratio

A benefit/risk assessment is included in the Clinical Hazard Assessment (Appendix C). The assessment concludes that "Review of the benefits derived by use of VR101 and the risks inherent in its use results in a conclusion that the benefits of device use outweigh the risks inherent in anticipated end-use and misuse situations."

8 STATISTICAL CONSIDERATIONS

CI03 and the following data analyses are designed to comply with the requirements of ICH E3, ICH E6, ICH E9, and with guidance from ICH E9 (R1), allowing the investigation to also support regulatory submissions and registrations in other countries or regions.

The formal Statistical Analysis Plan (SAP) will be completed prior to database lock and unblinding of the of the study data.

8.1 Statistical Hypotheses

8.1.1 Primary Efficacy

- The primary efficacy analysis will be a superiority comparison between the proportion of participants in each group who report FSFI-LD (lubrication domain composite) scores of 4.5 or greater after using VR101 or the sham ring for 4 weeks.

- This endpoint will reflect changes in FSFI-LD from baseline (Day 0) to the study endpoint (Day 28 ± 2). Inclusion criteria were designed to ensure that all study participants enter the study at a dysfunctional level as outlined in Section 6.3. The null hypothesis to be tested is that similar numbers of women in each of the study groups will report FSFI-LD scores of 4.5 or greater (non-dysfunctional) after 4 weeks of exposure to VR101 or the

sham device. The planned test statistic is a test for the difference between two proportions, $\alpha = 0.05$, two-tailed. Rejection of the null hypothesis will be interpreted as support for the alternative hypothesis, that there is a non-random, statistically significant effect (efficacy) for VR101.

$$H_O: \mu_{VR101} = \mu_{sham} \qquad H_A: \mu_{VR101} \neq \mu_{sham}$$

8.1.2 Exploratory

An exploratory analysis of individual changes in the Female Sexual Function Index (FSFI) total composite score (Rosen 2000) and its domains (Desire, Arousal, Lubrication, Orgasm, Satisfaction, and Pain) during 28 days of use will be conducted. Similar to the analyses conducted by Rosen 2000, changes in individual scores will be compared for the two groups using appropriate parametric (independent-test) or nonparametric (Mann-Whitney) statistical methods.

8.2 Analysis Groups

8.2.1 Target population

This is the stratum of subjects who are able to adhere to treatment, in other words, the subset of the broader population who would adhere to either treatment being compared, in which failure to adhere to treatment would not occur. The representative study target population is women with deficient vaginal moisture / lubrication who can independently and consistently use a vaginal ring, identified through inclusion and exclusion criteria and successful completion of the 4-week treatment phase of the study.

8.2.2 Full Analysis Set (ITT)

Includes all randomized subjects.

8.2.3 Modified ITT

As close as possible to including all randomized subjects, with the assumption that preservation of randomization provides the best foundation for statistical comparisons. Any modification to the full analysis set will be determined *a priori* based on specific experience, prior to data lock and unblinding.

8.2.4 Complete Case Set

The subset of subjects in the full analysis or ITT set who complete all study visits and for whom all outcome measures are available.

8.2.5 Per Protocol Analysis

The subset of subjects in the full analysis or ITT set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of study intervention according to the underlying study model, all inclusion and exclusion criteria, device use, responses and

complete study visits listed in Table 7, Schedule of Events. Protocol violations and deviations will be addressed in a way that is less biased and more interpretable and provides more information than naïve analysis of the per-protocol set. A complete demographic and baseline measure profile will be obtained for each participant at Enrollment (Day 0) and protocol compliance will be assessed weekly. Detailed explanations for non-compliance or failure to complete the study will be collected.

8.3 Sample Size Determination (ICH E3; 9.7.2 ICH E9; 3.5)

- As noted in Section 6.3.1, effect size and variability for this study were estimated from previous experience with VR101 and the literature on FSFI use in similar populations. The primary efficacy endpoint, group difference in proportion of subjects whose FSFI-LD scores exceed 4.5 (responders) at the end of the 4-week treatment period assuming a Sham Group responder rate of 30% and a VR101 responder rate of at least 64%, alpha = 0.01 was used for power and sample size calculations.
- The assumed effect size was based on previous studies with VR101 and a sham ring using self-reported measures of vaginal lubrication during intercourse (Section 6.3.1). The sample size needed to detect a 0.46 effect size while maintaining the probability of correctly rejecting the null hypothesis when it is false (power = 1 – beta) was calculated using the power and sample size function for a test between two proportions in Minitab 17 (Minitab 2017) computer software for prospective study design.
- Based on the power curves generated using this information and expected dropout rates (Section 8.4), a minimum of 80 subjects randomized to each group (VR101 or sham) of the study will provide adequate power for the primary efficacy analysis and continued safety evaluation. Robustness of the proposed sample size is justified by the considerable uncertainty that exists for expected variance in the FSFI-LD for this study.

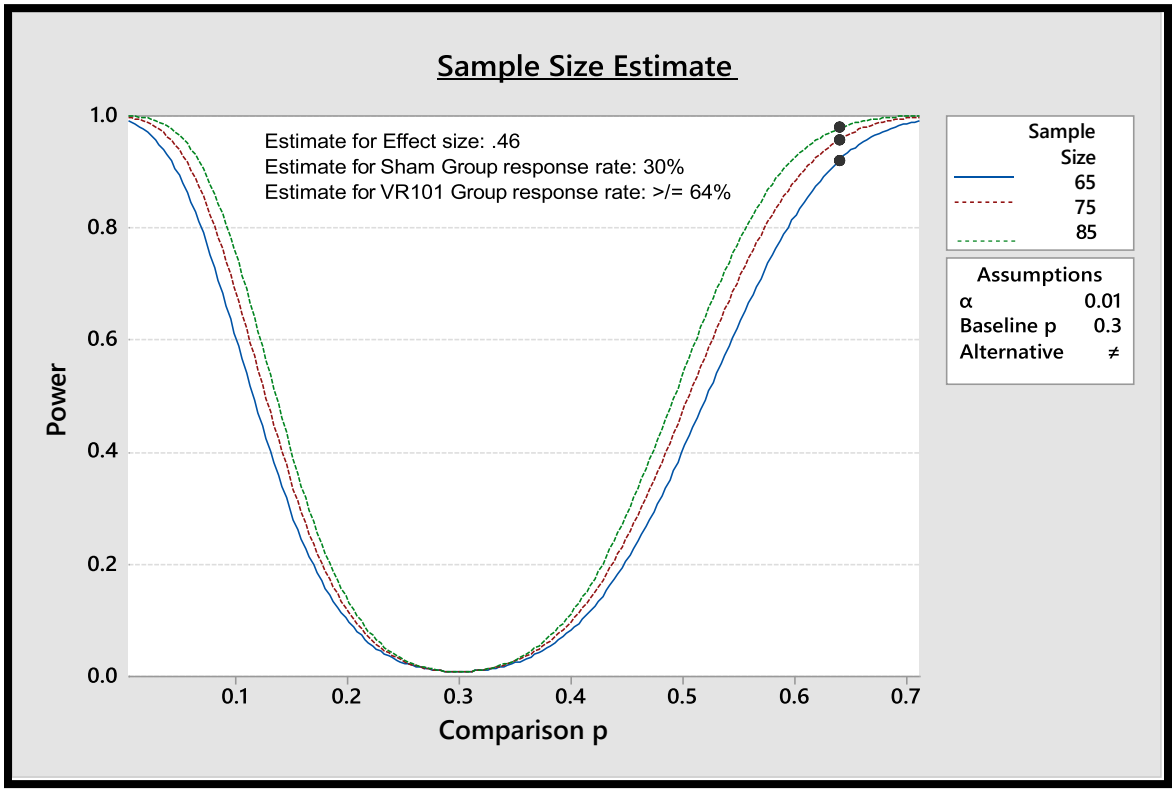

Figure 4. Robustness of the proposed sample size

8.4 Expected Drop-Out Rates

Based on experience with the VR101 in previous clinical investigation studies, we anticipate that approximately 70% of subjects screened for the study will meet inclusion/exclusion criteria and be enrolled, 95% of those enrolled will be randomized to treatment groups and is it estimated that of randomized subjects will complete the study, per protocol.

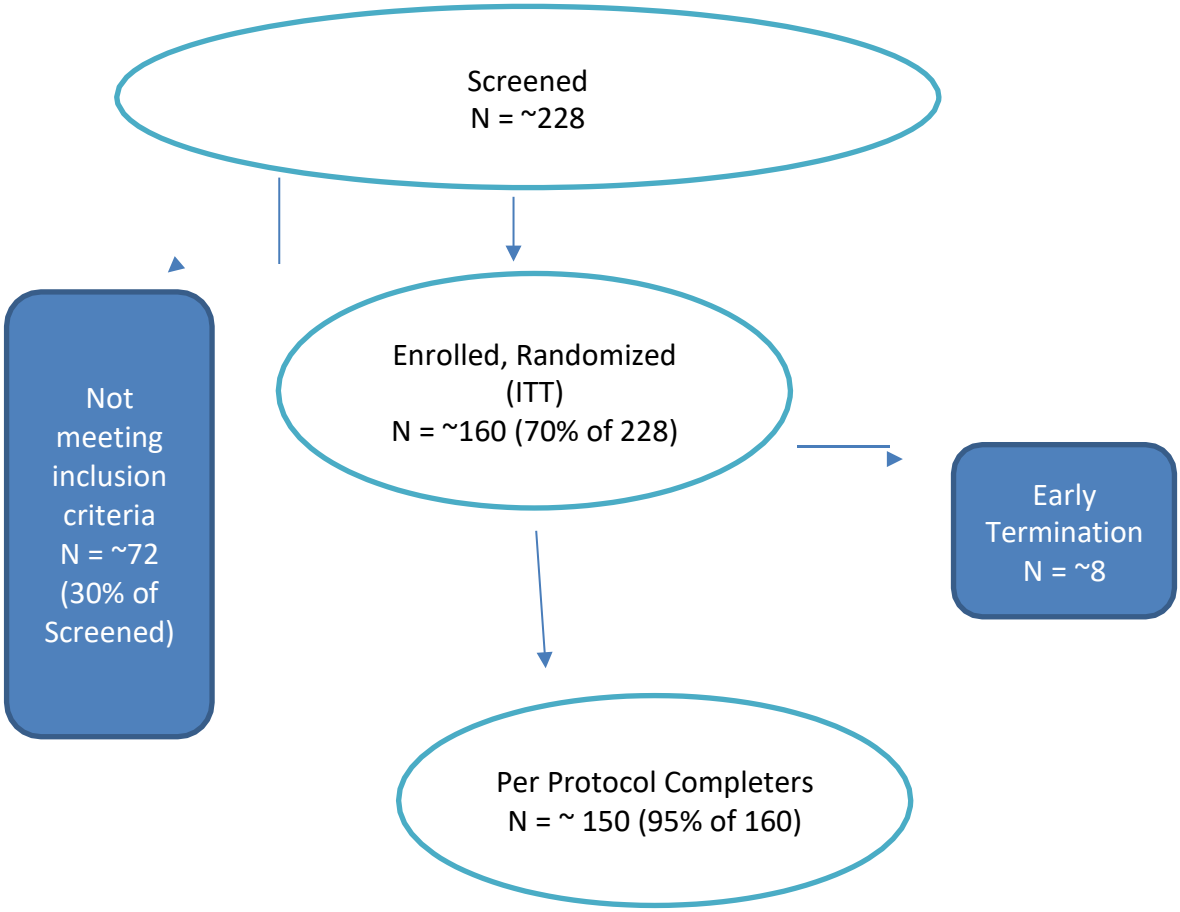

Figure 5. Estimation of participant distribution and drop-out rates

8.5 Pass / Fail Criteria of the Clinical Investigation

Demonstration of a statistically significant difference (at a 95% confidence level) between the study groups for proportions of subjects scoring 4.5 or higher on the FSFI-LD following the 4-week treatment phase.

8.6 Adjustment for Multiplicity

No adjustment for multiplicity is planned as only one hypothesis will be tested.

8.7 Disposition of Missing Data (ICH E3; 9.7.1, 11.4.2.2 ICH E9; 5.3. EMA Guideline on Missing Data in Confirmatory Clinical Trials, ICH E9 (R1) addendum)

8.7.1 Prevention of Missing Data

- Prevention of missing data is a primary aim of this study design. Subjects will be counseled at enrollment on the importance of completing the study and

communicating all issues and concerns to the study coordinator. In turn, the study coordinator will provide a "safe" place for disclosure of intent to withdraw from the study so that an Early Termination visit and final outcome measures can be collected prior to withdrawal of consent. As long as patient safety is assured, non-compliance will not require early discontinuation.

- The importance of completeness and quality of data and standardized procedures for handling potential dropouts will be emphasized during directed training of investigators and clinic/study personnel. Attrition will not be encouraged.
- Case report forms (CRFs) will be designed to capture relevant background information as well as objective reasons for early discontinuation when it cannot be prevented.

8.7.2 Incentive to Complete

- Under the FDA guidance for payment and reimbursement to research subjects, (January 2018) the sponsor will provide a study completion bonus equal to the payment for one regular study visit for subjects who complete the study per protocol (with no missing data).
- Participants who complete the 4-week double-blind study will be given an opportunity to continue in a 2-week open-label extension where they will be guaranteed to receive VR101.

8.7.3 Unavoidable Loss of Data

- It is understood that data may still be missing, for anticipated and unanticipated reasons (intercurrent events) that arise during the study. As no universally applicable methods for handling missing values are recommended in the guidance documents, methods for handling missing values in this study will be justified by reasons for missingness and predefined by updating this aspect in the statistical analysis plan during the blind review. An investigation will be made concerning the sensitivity of the results of analysis to the method of handling missing values.

  It is expected that any study subject who begins one of the treatment arms following randomization will be included in the primary efficacy analysis. As noted, randomization criteria require all inclusion criteria are met and that screening (Day 0) FSFI-LD scores are complete. The primary efficacy outcome, proportion of subjects who have a "functional" score of 4.5 or more after 4 weeks of treatment, is therefore dependent on a post randomization FSFI-LD score.

- Where unavoidable, participants who cannot complete 28 days of treatment will be scheduled for an End of Treatment visit so that final FSFI-LD scores can be collected prior to withdrawal of consent.

- For subjects who must drop out prior to providing study endpoint efficacy data the reason for early discontinuation will be ascertained and recorded in the CRF. Prior to data lock and unblinding of the randomization code the status and quality of each subject's study data will be assessed by the sponsor's data quality team. The disposition and assignment of each subject to a study population analysis group will occur prior to unblinding.

- Where final FSFI-LD data are not available and exceed greater than 5% of the values for comparison, a mixed model regression analysis that includes the dependent variable and one or more auxiliary variables that reflect plausible assumptions around the uncertainty due to missing data will be conducted and subjected to sensitivity analysis.

8.7.4 Missing Data by Groups

- The reasons why data are missing and whether there are systematic differences in the patterns of missing data across the treatment arms will also be summarized. Group differences will be examined following unblinding using a data summary table for the analysis groups. This information will be used to determine the most appropriate sensitivity analyses to test assumptions of the mixed model regression approach for missing data.

8.8 Planned Sensitivity Analyses

We will assess robustness of the findings based on the ITT or MITT analysis using comparison of results under different reference-based assumptions about the missing values. The final comparison analyses and associated assumptions will depend on the nature and patterns of missing data. These methods will be specified prior to breaking the randomization code for analysis.

8.9 Final Data Validation and Subject Disposition Determination

Prior to breaking the randomization code, the designated data review committee and study monitor will review all case records and determine subject disposition, assignment to subgroups for data analysis, method of dealing with any missing data, and relevant sensitivity analyses for alternate approaches.

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.

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 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.

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 and whether or not Device Related, must be recorded using the Adverse Event Form. 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 ring).

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 during CI03:

- 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
- Infection (e.g., Bacterial Vaginosis, Yeast Infection, Urinary Tract Infection)

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/pain

- Device-related cramping
- 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/urethral irritation/inflammation
- Device-related malodor
- Device-related vaginal discharge (e.g., excessive lubrication / secretions)
- Device-related incontinence
- Intermittent Nausea
- Intermittent Headache
- Physical interference with other intravaginal or intrauterine devices

Some anticipated ADEs listed above are hypothetical, and some have been observed clinically. Refer to reports for CI01 and CI02 for a complete list of observed ADEs (either definitely or potentially related to VR101 use) and their frequency.

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
- Device is not biocompatible

Per the Clinical Hazard Assessment, the residual risks associated with the above device deficiencies are adequately mitigated and/or are outweighed by the potential Clinical Benefits of VR101.

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.

AE collection will begin after consent has been obtained and continue until the final visit. Every AE or symptom will be recorded in the CRF and will include:

- Nature (Brief Description)
- Date and Time of onset
- Date and Time of resolution
- Severity
- Probability of relationship to study procedures
- Probability of relationship to the investigational device
- Action Taken
- Outcome

Based on the occurrence and intensity of AEs, coupled with results of any other observations, the Investigator, at his/her discretion and following discussion with the Sponsor, may decide to withdraw a subject or prematurely end the study for reasons of

clinical safety. The date of such termination will be recorded, and appropriate treatment instituted at the discretion of the Investigator or sub-Investigator.

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 (5) 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.

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 (STOPPING RULES)

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.

Further, the Sponsor may terminate the study at any time in a center:

- if the investigator is non-compliant with the protocol, the regulatory requirements or the ICH-GCP;
- if the CRF completion or drug accountability is inadequate, and the investigator is unable to take corrective action in any of these cases, or;
- in case of failure to recruit subjects.

If an unwanted effect (adverse reaction) is considered severe by the Investigator and endangers the health of all subjects, the study will be discontinued after agreement with the Sponsor.
The entire study may be terminated for medical reasons. In addition, the Sponsor retains the right to end the study at any time if the study cannot be carried out as agreed upon in the study protocol. In case of premature termination, the Investigators, IRBs and regulatory authorities will be informed by the Sponsor.
The Sponsor also reserves the right to terminate the study at any time for administrative reasons. The Sponsor will not reimburse the Investigator for the evaluation of subjects if the evaluations are conducted in a manner other than that specified in this protocol.

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

Bachman GA, Notelovitz M, Gonzalez, SJ, Thompson, C, Morecraft, BA. "Vaginal Dryness in Menopausal Women: Clinical characteristics and Nonhormonal Treatment." *Clinical Practice in Sexuality,* 1991; 7(9): 25-32.

Bachmann GA, Notelovitz, M, Kelly, SJ, Owens, A, Thompson, C. "Long Term Nonhormonal treatment of Vaginal Dryness." *Clinical Practice in Sexuality,* 1992; 8(8/9): 3-8.

Minitab 17 Statistical Software (2010). [Computer software]. State College, PA: Minitab, Inc. (www.minitab.com).

Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, Ferguson D, D'Angostino R Jr. "The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function." *Journal of Sex & Marital Therapy,* 2000 Apr-Jun; 26(2): 191-208.

Wiegel M, Meston C, Rosen R. "The Female Sexual Function Index (FSFI): Cross-Validation and Development of Clinical Cutoff Scores." *Journal of Sex & Marital Therapy*, 2005; 31(1), 1-20.

Appendix A
FSFI Survey and Scoring Method

(Note: Appendix A is 10 pages long including this page)

Female Sexual Function Index (FSFI) ©

Subject Identifier_____ Date _____

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION.

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how **often** did you feel sexual desire or interest?

   - ☐ Almost always or always
   - ☐ Most times (more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (less than half the time)
   - ☐ Almost never or never

2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?

   - ☐ Very high
   - ☐ High
   - ☐ Moderate
   - ☐ Low
   - ☐ Very low or none at all

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Almost always or always
   - ☐ Most times (more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (less than half the time)
   - ☐ Almost never or never

4. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Very high
   - ☐ High
   - ☐ Moderate
   - ☐ Low
   - ☐ Very low or none at all

5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Very high confidence
   - ☐ High confidence
   - ☐ Moderate confidence
   - ☐ Low confidence
   - ☐ Very low or no confidence

6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Almost always or always
   - ☐ Most times (more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (less than half the time)
   - ☐ Almost never or never

7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Almost always or always
   - ☐ Most times (more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (less than half the time)
   - ☐ Almost never or never

8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Extremely difficult or impossible
   - ☐ Very difficult
   - ☐ Difficult
   - ☐ Slightly difficult
   - ☐ Not difficult

9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Almost always or always
   - ☐ Most times (more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (less than half the time)
   - ☐ Almost never or never

10. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

    - ☐ No sexual activity
    - ☐ Extremely difficult or impossible
    - ☐ Very difficult
    - ☐ Difficult
    - ☐ Slightly difficult
    - ☐ Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

13. Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

17. Over the past 4 weeks, how **often** did you experience discomfort or pain <u>during</u> vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

18. Over the past 4 weeks, how **often** did you experience discomfort or pain <u>following</u> vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Very high
- ☐ High
- ☐ Moderate
- ☐ Low
- ☐ Very low or none at all

Thank you for completing this questionnaire

FSFI SCORING APPENDIX

Question	Response Options
1. Over the past 4 weeks, how **often** did you feel sexual desire or interest?	5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never
2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?	5 = Very high 4 = High 3 = Moderate 2 = Low 1 = Very low or none at all
3. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse?	0 = No sexual activity 5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never
4. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?	0 = No sexual activity 5 = Very high 4 = High 3 = Moderate 2 = Low 1 = Very low or none at all
5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?	0 = No sexual activity 5 = Very high confidence 4 = High confidence 3 = Moderate confidence 2 = Low confidence 1 = Very low or no confidence
6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?	0 = No sexual activity 5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never

7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?	0 = No sexual activity 5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never
8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?	0 = No sexual activity 1 = Extremely difficult or impossible 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?	0 = No sexual activity 5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never
10. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?	0 = No sexual activity 1 = Extremely difficult or impossible 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?	0 = No sexual activity 5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never
12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)?	0 = No sexual activity 1 = Extremely difficult or impossible 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult

13. Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

0 = No sexual activity
5 = Very satisfied
4 = Moderately satisfied
3 = About equally satisfied and dissatisfied
2 = Moderately dissatisfied
1 = Very dissatisfied

14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?

0 = No sexual activity
5 = Very satisfied
4 = Moderately satisfied
3 = About equally satisfied and dissatisfied
2 = Moderately dissatisfied
1 = Very dissatisfied

15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?

5 = Very satisfied
4 = Moderately satisfied
3 = About equally satisfied and dissatisfied
2 = Moderately dissatisfied
1 = Very dissatisfied

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

5 = Very satisfied
4 = Moderately satisfied
3 = About equally satisfied and dissatisfied
2 = Moderately dissatisfied
1 = Very dissatisfied

17. Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration?

0 = Did not attempt intercourse
1 = Almost always or always
2 = Most times (more than half the time)
3 = Sometimes (about half the time)
4 = A few times (less than half the time)
5 = Almost never or never

18. Over the past 4 weeks, how **often** did you experience discomfort or pain following vaginal penetration?

0 = Did not attempt intercourse
1 = Almost always or always
2 = Most times (more than half the time)
3 = Sometimes (about half the time)
4 = A few times (less than half the time)
5 = Almost never or never

19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?

0 = Did not attempt intercourse
1 = Very high
2 = High
3 = Moderate
4 = Low
5 = Very low or none at all

FSFI DOMAIN SCORES AND FULL SCALE SCORE

The individual domain scores and full scale (overall) score of the FSFI can be derived from the computational formula outlined in the table below. For individual domain scores, add the scores of the individual items that comprise the domain and multiply the sum by the domain factor (see below). Add the six domain scores to obtain the full scale score. It should be noted that within the individual domains, a domain score of zero indicates that the subject reported having no sexual activity during the past month. Subject scores can be entered in the right-hand column.

Domain	Questions	Score Range	Factor	Minimum Score	Maximum Score	**Score**
Desire	1, 2	1 – 5	0.6	1.2	6.0	
Arousal	3, 4, 5, 6	0 – 5	0.3	0	6.0	
Lubrication	7, 8, 9, 10	0 – 5	0.3	0	6.0	
Orgasm	11, 12, 13	0 – 5	0.4	0	6.0	
Satisfaction	14, 15, 16	0 (or 1) – 5	0.4	0.8	6.0	
Pain	17, 18, 19	0 – 5	0.4	0	6.0	
			Full Scale Score Range	2.0	36.0	

Appendix B
VR101 Investigational Labeling / Instructions for Use

(Note: Appendix B is 11 pages long including this page)

REVISION LOG

Rev	Eff. Date	CO	Brief Description of Change	Author
00	17-03-31	2017-06	Original approval and implementation	pT
01	21-01-2020	CR-0005	Update J3 Bioscience Address, Revised Warning for Pregnancy / Breastfeeding	JTC

Distribution List

- ☐ **Document Control**
- ☐ **R and D**
- ☐ **Manufacturing**
- ☒ **Quality Assurance**
- ☒ **Regulatory**
- ☒ **Clinical**
- ☐ **Cust. Svc/ Purchasing**
- ☐ **Management**
- ☐ **Lubrizol/ Vesta**
- ☐ **Purchasing**

Control Status of This Document:

Controlled

Document must be marked as Original, Controlled, Uncontrolled or Draft

1.0 Part Number LBL 001

2.0 Name VR101 Single-Unit Label- for devices used in clinical investigations

3.0 Description

Label to be affixed to packaged VR101 devices for exclusive use in clinical investigations

4.0 General Requirements

4.1 Color: black lettering/graphics on white label

4.2 Description, Label Dimensions, and Graphics (markings) per following table:

Product Code	Description & Label Size	Graphic
LBL 001	Single-Unit Pouch Label with Pressure-Sensitive Adhesive Backing **3.3"** **X** **4.0"** (Label Stock: Avery PN 8164)	**<u>VR101 Vaginal Lubrication Ring</u>** *Manufactured by: J3 Bioscience, Inc.* *825 North 300 West, Suite N231, Salt Lake City, Utah 84103* 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. Do not use if pregnant or breast feeding. Store at room temperature. LBL 001 R01 2020-01 Expiration Date: **SEE INSTRUCTIONS FOR USE**

4.3 Manufacturing

4.3.1 Label stock will be provided in sheets, 4 labels per sheet
4.3.2 Text and Marking will be printed using a laser printer

4.4 Cosmetics
4.4.1 Text and markings are to be clear and legible

5.0 Packaging and Labeling

5.1 Paper Stock (Avery Product)

5.1.1 Provided in packaging to protect labels from damage during transit

5.1.2 Labeled to identify contents

5.2 Printed Labels
5.2.1 Either apply directly to clinical product, or package in clean Zip Lock (or equivalent) bags

6.0 Special Requirements

None

7.0 Shelf Life

None known

8.0 Inspection and Sampling

8.1 If purchased with Purchase Order, verify that Purchase Order, packing slip and product packaging identify item as J3 Bioscience PN 002, Lot Number, PO Number, Quantity, and Manufacturing Date.

8.1.1 Certificate of Compliance is received with order and has been signed and dated by supplier representative.(Not Applicable)

8.1.2 Qualification Requirements:

- ❒ First Article Inspection
- ☐ Supplier Survey
- ☐ Vendor Site Visit
- ☐ Material Certification
- ☐ Certification of Compliance
- ☐ GMP Certification

- ☐ MSDS
- ☐ Other: _____

8.1.3 Inspection Requirements:

Each lot to be inspected

Sample Size:

- ☐ AQL 2.5 C = 0
- ☐ 100%
- ❒ N = 1
- ❒ Other: Verify Avery Part No. of label stock
- ❒ Verify Color of printed label
- ❒ Verify text and markings are as indicated in table appearing in Section 4.2.

8.1.4 Inspection Protocol

8.1.4.1 Documentation Verification

Assure correct Avery Part Number of label stock.

8.1.4.2 Material Inspection

Not required

8.2.3.3 Acceptance Criteria

Label roll stock must be correct Avery Part Number

Text and markings must be as indicated

Text and markings must not become illegible when attempts are made to rub them off by applying manual pressure with a thumb while moving thumb across the label.

8 Storage and Handling Requirements

Store indoors, away from sources of light and heat until applied to pouches.

10.0 Acceptable Suppliers

NOTE: SUPPLIER IDENTIFICATION IS FOR J3B USE ONLY (NOT TO BE DISTRIBUTED TO SUPPLIERS). Acceptable suppliers are to be identified on the last (separate) page of the Part Specification. This page is not to be used or referenced when obtaining quotes from potential suppliers or copied to existing suppliers.

Acceptable Suppliers

Any supplier of Avery Products

REVISION LOG

Rev	Eff. Date	CO	Brief Description of Change	Author
00	17-03-31	2017-06	Original approval and implementation	pT
01	21-01-2020	CR-0005	• Updated Study Contact Numbers from CI02 to CI03 • Corrected to reflect non-collection of used rings per CI03 CIP R01	JTC

Distribution List

- ☐ **Document Control**
- ☐ **R and D**
- ☐ **Manufacturing**
- ☒ **Quality Assurance**
- ☒ **Regulatory**
- ☒ **Clinical**
- ☐ **Cust. Svc/ Purchasing**
- ☐ **Management**
- ☐ **Lubrizol/ Vesta**
- ☐ **Purchasing**

Control Status of This Document:

Controlled

Document must be marked as Original, Controlled, Uncontrolled or Draft

1.0 Part Number LBL 002

2.0 Name VR101 Instructions for use- for devices used in clinical investigations

3.0 Description

IFU (Instructions for Use) to be affixed to or accompany VR101 devices used in CI 02.

4.0 General Requirements

4.1 Color: black lettering/graphics on white label

4.2 Description, Label Dimensions, and Graphics (markings) per following table:

Product Code	Description & Label Size	Graphic
LBL 001	IFU printed on either standard white paper or on white paper with pressure-sensitive adhesive backing. Preferred Dimensions are 8.5 x 11” Other dimensions are acceptable, as long as print is ≥ 8 pt font.	See Next Page for text of IFU

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.

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.

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

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

4.3 Manufacturing

4.3.1 Text and Marking will be printed using a laser printer.

4.4 Cosmetics

4.4.1 Text and markings are to be clear and legible.

5.0 Packaging and Labeling

5.1 Paper Stock (plain paper or paper with pressure-sensitive adhesive backing)

5.1.1 Provided in packaging to protect labels from damage during transit.

5.1.2 Labeled to identify contents

5.2 Printed Labels

5.2.1 Either apply directly to clinical product (paper stock with adhesive backing) or provide as inserts with product (plain paper) or independently (plain paper).

6.0 Special Requirements

None

7.0 Shelf Life

None known

8.0 Inspection and Sampling

8.1 When purchased with Purchase Order, verify that Purchase Order, packing slip and product packaging identify item as J3 Bioscience PN 002, Lot Number, PO Number, Quantity, and Manufacturing Date.

8.1.1 As appropriate, verify Certificate of Compliance is received with order and has been signed and dated by supplier representative.

8.1.2 Qualification Requirements:

- ❒ First Article Inspection
- ☐ Supplier Survey
- ☐ Vendor Site Visit
- ☐ Material Certification
- ☐ Certification of Compliance
- ☐ GMP Certification
- ☐ MSDS

☐ Other: _____

8.1.3 Inspection Requirements:

Each lot to be inspected

Sample Size:

☐ AQL 2.5 C = 0
☐ 100%
❒ N = 1
❒ Other: Verify Color of printed label
❒ Verify text and markings are as indicated in Section 4.2.

8.1.4 Inspection Protocol

8.1.4.1 Documentation Verification

Not required

8.1.4.2 Material Inspection

Not required

8.2.3.3 Acceptance Criteria

Text and markings must be as indicated

Text and markings must not become illegible when attempts are made to rub them off by applying manual pressure with a thumb while moving thumb across the label.

8 Storage and Handling Requirements

Store indoors, away from sources of light and heat until used.

10.0 Acceptable Suppliers

NOTE: SUPPLIER IDENTIFICATION IS FOR J3 Bio USE ONLY (NOT TO BE DISTRIBUTED TO SUPPLIERS). Acceptable suppliers are to be identified on the last (separate) page of the Part Specification. This page is not to be used or referenced when obtaining quotes from potential suppliers or copied to existing suppliers.

Acceptable Suppliers of labels are any suppliers of Avery Products.

Appendix C

VR101 Clinical Hazard Assessment

(Note: Appendix C is 14 pages long including this page)

J3 Bioscience, Inc.	**Title:** Clinical Hazard Assessment VR101	**Doc. #:** CHA 01 **Rev:** 00

Rev	Eff. Date (yymmdd)	CO	Brief Description of Change	Author
00	190325	2019-03	New Release	pT

Participants in this risk assessment:

Function	Title	Name
Management	CEO	R Tyler McCabe, PhD
R&D/Engineering	Engineer II (Consultant)	Justin Clark, PhD
Regulatory/ Quality	Consultant	Phil Triolo, PhD, RAC
Clinical	Advisor	Margit Janat-Amsbury, MD

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- ☒ **Management**
- ☐

Control Status of This Document:

Original

Document must be marked as Original, Controlled, Uncontrolled or Draft

Hazards Associated with use of VR101, and Verification or Validation that Hazards are Acceptably Mitigated to Justify placing VR101 on the market			
Hazardous Condition	**Potential Effect**	**Mitigation Method/ Verification that Method has been Implemented**	**Verification or Validation that Potential Hazards are Reduced to Acceptable Levels and Users are Adequately Informed of Residual Risks**
1. Energy Hazards			
Heat exposure	Device deformed or damaged	Under anticipated typical end use conditions and conditions of transport and storage, device materials are not known to degrade. Shelf life studies per P02	R02 VR101 Shelf Life Evaluation Residual Risk: None to report to end users
Radiation exposure (exposure to x-rays, MRI, other diagnostic imaging procedures)	Material degraded or discolored or Release rate altered	Device contains no ferromagnetic materials (and is therefore MRI compatible) and is unlikely to be damaged by brief exposures to low-level radiation	No validation necessary; radiation exposure is not a risk. Residual Risk: None to report to end users
2. Biological Hazards			
High level of bioburden on product	Infection	Product is manufactured and packaged in a controlled environment by an ISO13485:2003-certified and FDA QSR-compliant facility. Routine monitoring of controlled environment demonstrates that	Results of Water Activity studies reported in CPTC M18-5862 demonstrate that the glycerol-based lubricating and packaging solutions do not support microbial growth (A_w is < 0.60). Results of bioburden enumeration studies conducted on packaged devices stored for up to 21 months demonstrate a low and acceptable bioburden. No viable organisms have been

Hazards Associated with use of VR101, and Verification or Validation that Hazards are Acceptably Mitigated to Justify placing VR101 on the market			
Hazardous Condition	**Potential Effect**	**Mitigation Method/ Verification that Method has been Implemented**	**Verification or Validation that Potential Hazards are Reduced to Acceptable Levels and Users are Adequately Informed of Residual Risks**
		environment is in a state of control and the potential for device contamination with viable organisms is low and acceptable.	detected on any packaged VR101 devices. See Bioburden GLP Report from NLI Study 1038660-S01. Residual Risk: None to report to end users
Unacceptably high level of pyrogens on product	Fever	Material-mediated pyrogen study per WuXi Protocol 900770-27 Toxicologic risk assessments of substances extracted from VR101.	Pyrogenic responses are not a significant concern for devices that are placed in the vagina. Nonetheless, results of a material-mediated pyrogenicity study (See GLP Report for NLI Study 113438-S01) demonstrate that the polymeric ring component of VR101 does not elicit a pyrogenic response, and a toxicological risk assessment (See Table 9 of Gad Consulting Services Report "Biological Safety Assessment of VR101 Lubricating Intravaginal Ring", dated 18 January 2019) concludes that the constituent materials of VR101 are not known to elicit a pyrogenic response. Residual Risk: Device is labelled "non-pyrogenic."
Device materials present an unacceptable biological risk	Toxic, immunology, or otherwise untoward biological response	Toxicologic risk assessments of substances extracted from VR101. Biocompatibility studies performed by NLI to meet ISO10993-1 requirements and FDA recommendations	Results of biological safety (biocompatibility) studies demonstrated low and acceptable biological and toxicological risks. See Gad Consulting Services Report "Biological Safety Assessment of VR101 Lubricating Intravaginal Ring", dated 18 January 2019. No biological or toxicological effects were seen or reported for any of the 21 participants in CI01 or 72 participants in CI02,

Hazards Associated with use of VR101, and Verification or Validation that Hazards are Acceptably Mitigated to Justify placing VR101 on the market			
Hazardous Condition	**Potential Effect**	**Mitigation Method/ Verification that Method has been Implemented**	**Verification or Validation that Potential Hazards are Reduced to Acceptable Levels and Users are Adequately Informed of Residual Risks**
			validating the low and acceptable biological and toxicological risk associated with VR101 use. See CI02-R, Section 5.5.1. Residual Risk: None to report to end users
3. Environmental Hazards			
Compatibility with other devices	Damage to condoms, damage to IUDs, damage to other IVRs (intravaginal rings) or other devices placed intravaginally	Condoms: Compatibility of VR101 lubricating solution evaluated per ASTM D7661-10. Other Intravaginal Rings: Residual risk of use of VR101 with other intravaginally placed devices will be documented. IUD (Intrauterine Device, e.g., ParaGard®) Residual risk of use of VR101 with other intravaginally placed devices will be documented	Results of studies performed per ASTM D7661-10 demonstrate the compatibility of VR101 lubricating solution with male polyurethane and natural rubber latex condoms and female FC2 Condoms. See Report R05. Residual Risk: IFU documents that the use of VR101 with other intravaginally placed devices has not been investigated. Residual Risk: IFU will document that the use of VR101 with other intravaginally placed devices has not been investigated.
Handling of the device	Damage to device, loss of product cleanliness, leak of package contents due to damage to product or	Risks associated with the transport and handling of the device are low, as the device is not provided sterile and, therefore, loss	Inspection procedures are in place to assure devices meet specifications before being released to the marketplace. See Final Release QA Procedure SOP 7.5-04.

Hazards Associated with use of VR101, and Verification or Validation that Hazards are Acceptably Mitigated to Justify placing VR101 on the market			
Hazardous Condition	**Potential Effect**	**Mitigation Method/ Verification that Method has been Implemented**	**Verification or Validation that Potential Hazards are Reduced to Acceptable Levels and Users are Adequately Informed of Residual Risks**
	packages, resulting in infection or change of rate of delivery of lubricant	of the integrity of the protective packaging is not critical to device function. Further, the device is robust, with no moving parts that could be damaged and damage to the product or packaging would be evident to end users. Therefore, the risk of damage to devices during transport is, by design, inherently low and acceptable	VR101 devices are lightweight and have no sharp edges or other characteristics that could puncture or otherwise compromise their primary packaging. Consequently, no tests were necessary to confirm the ability of the primary packaging to protect the devices. Further damage to the package is obvious to end user and the user is instructed to inspect packaging for damage before use, and to not use product if damage is apparent. Residual Risk: The user is instructed to inspect packaging for damage before use, and to not use product if damage is apparent.
Adverse storage condition	Loss of product cleanliness, leakage of fluid due to damage to product or packages, material degradation	See above: Risks associated with storage of the device in adverse storage conditions are low, as the device is not provided sterile and, therefore, loss of the integrity of the protective packaging is not critical to device function.	Damage to package is obvious to end user and user is instructed to inspect package for damage before use, and to not use product if damage is apparent. Residual Risk: The user is instructed to inspect packaging for damage before use, and to not use product if damage is apparent. Residual Risk: The device is labeled with the symbol for “Keep dry.”
4. Labeling Hazards			

Hazards Associated with use of VR101, and Verification or Validation that Hazards are Acceptably Mitigated to Justify placing VR101 on the market			
Hazardous Condition	**Potential Effect**	**Mitigation Method/ Verification that Method has been Implemented**	**Verification or Validation that Potential Hazards are Reduced to Acceptable Levels and Users are Adequately Informed of Residual Risks**
Inadequate labeling	Information on label is inadequate, lacks clarity or readability, and results in device misuse.	Inspection of labeling for integrity and legibility Query of users during CI01 and CI02 on the ability to use the device by following the provided instructions for use	Responses to Questionnaire used in CI01 demonstrated users' ability to follow provided directions and use device correctly after reading the IFU and having any concerns clarified by clinical investigation staff. Responses to Questionnaire used in CI02 demonstrated users' ability to follow provided directions and use device correctly after reading the IFU without any input from clinicians or others. See Report CI02-R, Section 5.5.3, Claim 2. Residual Risk: Labels include the symbol for directing the user to See Instructions for Use.
Inadequate or wrong information in IFU	Incorrect use of the device	Query of users during CI01 and CI02 on the ability to use the device by following the provided instructions for use	Responses to Questionnaire used in CI01 demonstrated users' ability to follow provided directions and use device correctly after reading the IFU and having any concerns clarified by clinical investigation staff. Responses to Questionnaire used in CI02 demonstrated users' ability to follow provided directions and use device correctly after reading the IFU without any input from clinicians or others. See Report CI02-R, Section 5.5.3, Claim 2. Residual Risk: Labels include the symbol for directing the user to See Instructions for Use.

Hazards Associated with use of VR101, and Verification or Validation that Hazards are Acceptably Mitigated to Justify placing VR101 on the market			
Hazardous Condition	**Potential Effect**	**Mitigation Method/ Verification that Method has been Implemented**	**Verification or Validation that Potential Hazards are Reduced to Acceptable Levels and Users are Adequately Informed of Residual Risks**
Missing IFU	IFU not available when needed	IFUs are affixed to each packaged device.	Final inspection procedures at contract manufacturer assure all devices are packaged with instructions for use. Residual Risk: None to report to end users
Allergic response to natural latex present in packaging	Skin irritation	Neither the packaging or device is constructed of materials containing natural rubber latex.	No verification required, as device is not constructed of materials containing natural rubber latex. Residual Risk: End user is informed that the device is not manufactured using natural rubber latex.
Allergic response to device materials	Allergic response, anaphylactic shock	Device is composed of materials that have not been shown to elicit an allergic response. Device evaluated for sensitization per WuXi protocol 900850-28.	Results of Sensitization study NLI 669632 demonstrate that the device/device materials are not sensitizers. Residual Risk: Device is contraindicated for use in individuals with known or suspected allergies to polyurethane or glycerol.
5. Use- and User-related Hazards			
Improper use of device	Device not placed properly, expulsion	Query of users during CI01 and CI02 on the ability to use the device by following the provided instructions for use.	Responses to Questionnaire used in CI01 demonstrated users' ability to follow provided directions and use device correctly after reading the IFU and having any concerns clarified by clinical investigation staff. Responses to Questionnaire used in CI02 demonstrated users' ability to follow provided directions and use device correctly after reading the IFU without any input from clinicians or others. See Report CI02-R, Section 5.5.3, Claim 2.

Hazards Associated with use of VR101, and Verification or Validation that Hazards are Acceptably Mitigated to Justify placing VR101 on the market			
Hazardous Condition	**Potential Effect**	**Mitigation Method/ Verification that Method has been Implemented**	**Verification or Validation that Potential Hazards are Reduced to Acceptable Levels and Users are Adequately Informed of Residual Risks**
			Residual Risk: None to report to end users
Reuse of contaminated device	Infection	Query of users during CI01 and CI02 on the ability to use the device by following the provided instructions for use.	Responses to Questionnaire used in CI01 demonstrated users' ability to follow provided directions and use device correctly after reading the IFU and having any concerns clarified by clinical investigation staff. Responses to Questionnaire used in CI02 demonstrated users' ability to follow provided directions and use device correctly after reading the IFU without any input from clinicians or others. See Report CI02-R, Section 5.5.3, Claim 2. Residual Risks: The IFU states that the device is for single use, only. Residual Risk: Instructions for use state that if a device is expelled, it may be rinsed off and reinserted.
Physical movement of device during activities	Irritation (mechanical)	Mechanical tests to assess device compressibility (STP 004.) Physical dimensions of the device are not significantly different from those of other currently marketed Intravaginal rings.	Results of mechanical tests to assess device compressibility (See R02-A) demonstrate the compressibility of the device is comparable to that of clinically acceptable devices. The physical dimensions of the device are verified before each lot is released (See QAP 001). Residual Risk: None to report to end users.

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Hazardous Condition	**Potential Effect**	**Mitigation Method/ Verification that Method has been Implemented**	**Verification or Validation that Potential Hazards are Reduced to Acceptable Levels and Users are Adequately Informed of Residual Risks**
Device releases too much lubricant	Leakage of vaginal fluids/glycerol solution, a user inconvenience resulting in lesser device use and persistence of medical conditions	STP-008 is followed to assure a consistent release rate *in vitro.* In CI01 and CI02, users were asked to rate their daily experience with the ring on a scale of 1 to 9, with a score of 5 representing a participant response that VR101 was providing the "right amount" of lubrication, and a score of 9 representing "too much" lubrication.	Results of *in vitro* release studies can be found in R02-D. In CI01, the mean daily experience score for the entire study population was 6.4 indicating that participants, on average, felt that the ring was providing sufficient, but marginally more lubrication than needed. See Report CI01-R. Participants in CI02 scored the release of lubricant favorably, see CI02-M01. Residual Risk: None to report to end users
Device is too rigid	Discomfort resulting in decreased or cessation of device use and persistence of medical conditions	Mechanical tests to assess device compressibility (STP-004.) In CI01 and CI02, participants were presented with the statement "The ring is comfortable to me today," and asked to record their agreement level on a scale of 0 to 4 (where 3 = "Agree a Lot" and 4 = "Agree	Results of mechanical tests to assess device compressibility (see R02-A) demonstrate the compressibility of the device meets specs and is comparable to that of clinically acceptable devices. For CI01, the mean agreement level of the study population ranged from 2.8 to 3.6 throughout the study, and was only less than 3 ("Agree a Lot") on 1 out of 14 study days. Furthermore, when participants were asked at each of the 3 clinical visits where the question was posed what they would change about VR101 during and following use, only 1 of 21 participants said that they would make the ring softer.

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Hazardous Condition	**Potential Effect**	**Mitigation Method/ Verification that Method has been Implemented**	**Verification or Validation that Potential Hazards are Reduced to Acceptable Levels and Users are Adequately Informed of Residual Risks**
		Completely") in their diaries.	Results of CI02 also indicate that users generally found the ring to be comfortable, see CI02-R, Section 5.5.3, Claim 3). Residual Risk: None to report to end users
Device is too small/soft	Device expulsion resulting in an inconvenience to user and potential for device contamination.	Mechanical tests to assess device compressibility (STP 004.) The physical dimensions of the device are not significantly different from other currently marketed IVRs.	Results of mechanical tests to assess device compressibility (See R02-A) demonstrate the compressibility of the device meets specs and is comparable to that of clinically acceptable devices. During CI01, only one device was expelled during the study of 21 participants (42 rings were inserted, validating that the ring isn't too small for most anticipated users. See Report CI01-R). Residual Risk: None to report to end users.
Device absorbs or emits substances with unpleasant odors or encourages the concentration of substances with unpleasant odors	Unpleasant odor, resulting in lesser device use and persistence of medical conditions	Participants in CI01 were asked to comment on odor, and reports of malodor were classified as adverse events in CI02	In CI01, participants were asked if they noticed any unusual vaginal odor at any time during the Ring was in place. Most participants (16 of 21, 76% of the population) reported "no odor at all," while 5 participants reported "a little odor." No participants reported noticing "a lot of odor." It should be noted that, no attempt was made to assess whether participants felt that this odor was related to Ring use, or a normal occurrence. In CI02, one report of mild malodor was reported in 890 ring uses that was deemed "possibly related" to ring use by clinical staff. Two other reports of malodor were reported but determined to be unrelated to ring use by clinical staff (see CI02-R, Section 5.1)

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			Residual Risk: None to report to end users. Ring-related malodor does not represent a harm to patient safety.
Chemical reaction with analytes of interest, or interaction with microbes	Interference with laboratory tests leading to possible misdiagnoses	No clinical assessments of the interference of the device with laboratory tests have been made.	No examinations or laboratory tests whose results could be corrupted by the presence of the device were conducted during CI01 or CI02. Reports in the clinical literature strongly indicate that the amount of glycerol present in the vagina will not affect relevant lab study results. Residual Risk: None to report to end users
Creation of environment favorable to microbial growth	Increased potential for infection	Devices are manufactured and packaged under clean, controlled conditions. The water activity of VR101 lubricating solution is low and does not support microbial growth.	Test results reported in CPTC M18-5862 demonstrate that the water activity of the VR101 lubricating solution remains at levels that do not support microbial growth (a_w<0.60) over the shelf life of the device. None of the bioburden study results, reported for packaged devices stored for up to 21 months, were positive for microbial growth. Samples have been retained for additional bioburden testing at longer storage durations. See Bioburden GLP Report from NLI Study 1038660-S01 None of the participants in CI01 reported any infections during the 3-week duration of the study, which included two weeks of device use and one week of assessment at the conclusion of the 2 weeks of use.

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Hazardous Condition	**Potential Effect**	**Mitigation Method/ Verification that Method has been Implemented**	**Verification or Validation that Potential Hazards are Reduced to Acceptable Levels and Users are Adequately Informed of Residual Risks**
			One infection was reported by a participant in CI02 which resolved when VR101 was removed. The participant continued on in the investigation and completed it with no lasting effects. Residual Risk: None to report to end users
Material failure due to mishandling	Release of ring contents	Tensile test per STP-005 Use of materials with known acceptable tensile properties Biocompatibility of VR101 device	Tensile tests confirm manufactured rings resist tensile forces much greater than those anticipated during use. See Report R02-B. Biocompatibility test results demonstrate risks associated with release of ring contents (lubricating solution) are low and acceptable. No VR101 mechanical failures were reported during CI01 (42 rings used, each for one week) or CI02 (a total of 890 devices and 275 shams used). See Reports CI01-R and CI02-R. Residual Risk: User is instructed to See Instructions for Use.

Hazards Associated with use of VR101, and Verification or Validation that Hazards are Acceptably Mitigated to Justify placing VR101 on the market			
Hazardous Condition	**Potential Effect**	**Mitigation Method/ Verification that Method has been Implemented**	**Verification or Validation that Potential Hazards are Reduced to Acceptable Levels and Users are Adequately Informed of Residual Risks**
VR101 is difficult to remove	Device is a foreign body that can induce infection	Mechanical tests to assess device compressibility (STP-004.) The physical dimensions of the device are not significantly different from other currently marketed IVRs. Biocompatibility of VR101 device.	Results of mechanical tests to assess device compressibility (See R02-A) demonstrate the compressibility of the device meets specs and is comparable to that of clinically acceptable devices. Biocompatibility test results demonstrate risks associated with a retained ring are low and acceptable (See Gad Consulting Services Report "Biological Safety Assessment of VR101 Lubricating Intravaginal Ring", dated 18 January 2019) During CI02, 6 of 72 participants had difficulty removing the ring. Residual Risk: IFU contains the following Warning: "Some women may find VR101 difficult to remove. If VR101 removal is difficult, a partner may assist. If removal by a partner is difficult, not possible, or painful, contact your healthcare provider for assistance."

Conclusions

1. All identified risks have been reduced as far as possible and residual risks have been identified to end users in the provided labeling.

2. Review of the benefits derived by use of VR101 and the risks inherent in its use results in a conclusion that the benefits of device use outweigh the risks inherent in anticipated end-use and misuse situations.