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

Original Date:	January 31, 2020
Revision	Rev. 00
Revision Date:	August 12, 2020
Effective:	August 12, 2020

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
Tel: 801-550-9956
Fax: 866-768-9341

OFFICE ADDRESS:
J3 Bioscience, Inc.
825 North 300 West, Suite N231
Salt Lake City, Utah 84103
Email: tmccabe@j3bio.com
Tel: 801-550-9956
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

Signatures of Approval of SAP (Revision 00)

This statistical analysis plan was subject to critical review and has been approved by the following:

Affiliation	Name	Signature	Date
J3 Bioscience President/CEO	R. Tyler McCabe, PhD	R. Tyler McCabe	12 Aug 2020
Biomedical Engineer II Consultant to J3 Bioscience	Justin T. Clark, PhD	Justin Clark	12 Aug 2020
Biostatistical Consultant to J3 Bioscience	Rita Hanover, PhD	Rita Hanover	12 Aug 2020

Table of Contents

LIST OF ABBREVIATIONS AND DEFINITIONS 5
1 INTRODUCTION 6
1.1 Purpose of the analyses 6
1.2 Study Design 6
1.3 Number of participants 6
1.4 Diagnosis and Key Inclusion Criteria for the study population 6
1.5 Study Schematic 7
1.6 Summary of Study Schedule 7
2 OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION 8
2.1 Study Objectives 8
2.2 Hypotheses of the Clinical Investigation 8
3 ENDPOINTS 8
3.1 Primary Endpoint 8
3.2 Safety Endpoints 10
3.3 Exploratory Endpoints 10
4 STUDY PARTICIPANTS 10
4.1 Sample Size determination 10
4.2 Procedures for Replacement of Participants 11
4.3 Randomization and Blinding 11
5 DATA COLLECTION AND MANAGEMENT 11
5.1 Interim Analysis 12
5.2 Deviations from the CIP 12
6 STATISTICAL ANALYSES 12
6.1 Primary Efficacy Analysis 12
6.2 Exploratory Analyses 13
7 ANALYSIS GROUPS 14
7.1 Full Analysis Set (ITT) and Modified ITT 14
7.2 Complete Case Set 14
7.3 Per Protocol Set 15
8 DISPOSITION OF MISSING DATA 15

8.1 Prevention of Missing Data 15
8.2 Incentive to Complete 15
8.3 Unavoidable Loss of Data 16
8.4 Missing Data by Groups 16
9 PLANNED SENSITIVITY ANALYSES 17
10 POST STUDY BLIND DATA REVIEW 17
10.1 Final Data Validation 17
10.2 Data Entry Verification 17
10.3 Data Quality and Reliability 18
10.4 Blind Data Review Results 18
10.5 Subject Assignment to Analysis Groups 20
11 REFERENCES 21
12 BLIND REVIEW SUMMARY TABLES 22

LIST OF ABBREVIATIONS AND DEFINITIONS

ADE	Adverse Device Event (Effect)
AE	Adverse Event
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CI01	Clinical Investigation 01 (Pilot)
CI02	Clinical Investigation 02 (Pivotal)
CI03	Clinical Investigation 03 (Supplemental)
CRA	Clinical Research Associate
CRF	Case Report Form
FDA	Food and Drug Administration of United States
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ISO	International Organization for Standardization
IVR	Intravaginal Ring
NSR	Non-Significant Risk
OHRP	Office of Human Research Protection
PI	Principal Investigator
SADE	Serious Adverse Device Event (Effect)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
USAE	Unanticipated Serious Adverse Event

1 INTRODUCTION

This document describes the planned statistical analyses for Protocol CI03 CIP **"CI03: A Clinical Investigation to Evaluate Efficacy of the J3 Bioscience Lubricating Intravaginal Ring VR101 as a Personal Lubricant Device in Women."** This analysis plan is meant to supplement the study protocol. Any deviations from this analysis plan will be described in the final clinical study report. In this revision (00), Section 10 describes the procedures and outcomes of the blind data review following all data collection and resulting revisions and additions to the original statistical analysis plan.

1.1 Purpose of the analyses

The data from CI03 will be used to support submission of a premarket 510(k) notification to the FDA to enable regulatory clearance of the device in the United States (US). The investigation and data analyses are designed to comply with the requirements of 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 investigation is designed to demonstrate the efficacy of the VR101 lubricating intravaginal ring (IVR) as a personal lubricant device, for vaginal application. The device is intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity and supplement the body's natural lubrication.

1.2 Study Design

This is a randomized, double-blind, sham-controlled, 4-week parallel group study with an optional 2-week open-label extension and 1-week safety follow-up. Participants will be randomized (1:1) into two groups for the study. One group will be assigned to use the active VR101 vaginal lubrication device and the other group will be assigned to use a sham ring that does not contain lubricant. The study is designed as a two-center trial with approximately equal enrollment at each site.

1.3 Number of participants

A minimum of 160 females will be randomized to VR101 or sham ring during the 4-week treatment phase of the study.

1.4 Diagnosis and Key Inclusion Criteria for the study population

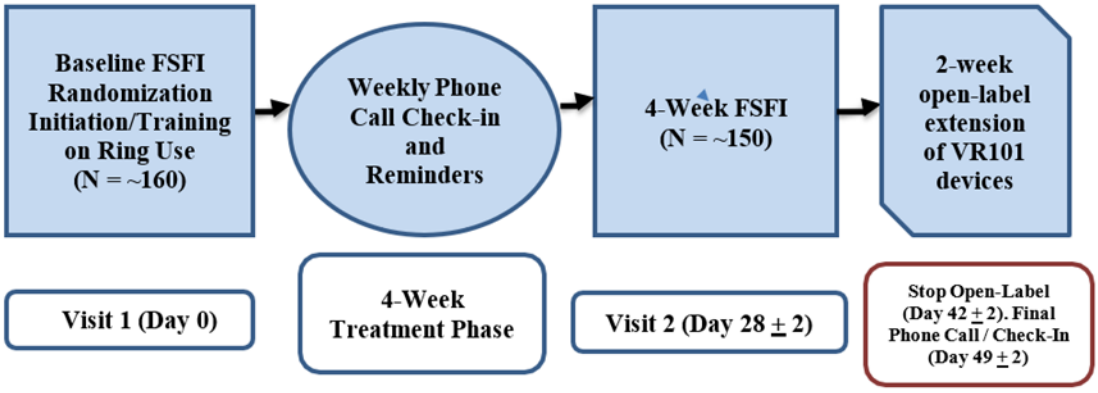
Sexually active women at least 21 years of age who report experiencing lack of vaginal lubrication during sexual intercourse will be screened for participation in the study. The key inclusion criteria are:

- Responses on the Female Sexual Function Index (FSFI) Lubrication Domain indicating dysfunctional level of vaginal lubrication during sexual intercourse.
- Willingness to comply with the study schedule, abstain from use of vaginal moisturizers, lubricants, lubricated condoms, other vaginally placed devices, and hormone replacement therapy, use of an approved method of contraception if appropriate, and attempt sexual intercourse at least 4 times during the 4-week treatment period.

- Ability to place and remove the IVR appropriately and independently.

A complete listing of inclusion and exclusion criteria is included in the CI03 Study Protocol effective January 31, 2020.

1.5 Study Schematic



1.6 Summary of Study Schedule

- After each 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. A four-week supply of assigned devices will be provided to each participant.

- Participants will be instructed to use the randomly assigned device continuously and exchange with a new device every 7 days.

- 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 device and insert a new one. During each call, information about compliance, including changes in

medications, use of lubrication products, frequency of sexual intercourse and oral sex and any health or issues they are having with the study device will be collected.

- Participants will return for a final study visit (Visit 2) on day 28 (+/-2 days). Participants will discontinue use of their device during the 28-day Visit and will return all unused devices. They will complete the Visit 2 FSFI at that time.

- Participants who complete the Visit 2 assessment will be offered two VR101 devices in a 2-week open label extension, followed by a final safety follow-up phone call 1 week after the end of the open label extension.

2 OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

2.1 Study Objectives

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.

2.2 Hypotheses of the Clinical Investigation

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).

3 ENDPOINTS

3.1 Primary Endpoint

The primary efficacy endpoint is the participant's score on the 4-item lubrication domain of the Female Sexual Function Index (FSFI) following 4 weeks of consecutive treatment with VR101 or a sham ring. The FSFI is a self-report survey validated to assess sexual function in women (Rosen, *et al*., 2000; Wiegel *et al*., 2005), supported by FDA as appropriate for evaluating VR101 efficacy. The FSFI contains 19 questions, divided in to 6 characteristic domains: Desire, Arousal, Lubrication, Orgasm, Satisfaction, and Pain. The Lubrication domain is directly relevant to the intended use for VR101. All participants admitted to the study will enter at a "dysfunctional" FSFI lubrication domain level. Following four weeks of treatment, participants with a score of 4.5 or better on the Lubrication domain will be considered "responders" and the proportion of responders in each group will be compared in the primary efficacy analysis.

The FSFI Lubrication domain includes 4 questions:

- Q7. 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

- Q8. 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

- Q9. 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

- Q10. 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

  Participants must answer these questions with a 1, 2, or 3 to be enrolled in the study at Visit 1. The upper bound of 3 ensures that all participants enter at a dysfunctional level of vaginal lubrication. After 4 weeks of consecutive use of VR101 or the sham IVR, it is expected that more of the participants in the VR101 group will have experienced a clinical degree of improvement in vaginal lubrication than those in the sham IVR group. In an FSFI cross-validation study (Wiegel *et al.,* 2005) a lubrication sub score threshold of 4.35 out of 6 was noted as an accurate discriminant of overall sexual dysfunction. The threshold for "responder" status for this study was set at 4.5 or greater because that is the next highest achievable score above 4.35. For lubrication domain scoring, responses to the four questions are summed and multiplied by a factor of 0.3. The lowest achievable FSFI-LD score for this study is 1.2 (as sexual activity is a required inclusion criteria, all 1 point responses, 4 x 0.3 = 1.2) and the highest score is 6 (all questions answered at 5 points, 20 x 0.3 = 6).

3.2 Safety Endpoints

All adverse events (AE) and adverse device events (ADE) as well as any Serious AEs or ADEs will be recorded throughout the study and will be assessed for severity and relatedness to VR101 use. Each type of event is described, and examples are listed in the CI03 CIP.

3.3 Exploratory Endpoints

- Change in FSFI subdomain scores from screening to completion of 4 consecutive weeks of treatment with VR101 or the sham IVR. Point responses (numerical responses) for the set of questions for each domain are summed and then multiplied by the indicated factor for that domain. Individual domain scores at Visit 1 will be subtracted from individual domain scores at Visit 2 to provide a change score. The mean change from baseline for each of the domains will be compared across the study arms using Student's *t*-test.

- Change in total FSFI score from screening to completion of 4 consecutive weeks of treatment with VR101 or sham. Total FSFI reflects overall sexual function and is the sum of all domain scores. The mean change from baseline in total FSFI score will be compared across the study arms using Student's *t*-test.

4 STUDY PARTICIPANTS

4.1 Sample Size determination

As VR101's efficacy has not been tested using the FSFI-LD, power and sample size for this study were estimated using parameters gleaned from previous experience with VR101 (CI01 and CI02, described in detail in the CI03 CIP) and published literature on FSFI use in studies with similar populations. For the primary efficacy analysis, statistical comparison of the proportion of participants in each group with a FSFI lubrication domain score of 4.5 or better (responders) at the end of the 4 week treatment period, a Sham group (placebo) responder rate of 30% was used as a starting point for the sample size determination. Given the considerable uncertainty for variability of the FSFI-LD scores and expected proportion of responders in the VR101 group the sample size was based on 0.90 power to detect a minimum 60% response rate at $\alpha = 0.01$. Based on the power curves generated using this information and expected dropout rates of around 5%, it was determined that a minimum of 160 participants (minimum 80 each group) would need to be randomized to provide 0.90 power for the primary efficacy analysis.

4.2 Procedures for Replacement of Participants

Participants may voluntarily withdraw from the investigation for any reason at any time. However, the participant must be queried as to their reason for withdrawal and, if consent has not been withdrawn an early termination visit scheduled for final FSFI and safety data collection, a pregnancy test if appropriate, and return of unused devices. As much detail as possible will be collected and the major reason for discontinuation will be recorded. Participants will not be replaced. All data collected from all participants will be reviewed prior to finalization of this SAP. Analysis groups and methods for addressing any missing data will be assigned and the final revision (00) of this SAP will be approved prior to unblinding.

4.3 Randomization and Blinding

All participants will receive a consecutive screening ID number upon signing the informed consent document. The screening numbers for each site (A and B) will start at 001 and run consecutively (001A through XXXA and 001B through XXXB). A binary computerized random number sequence will be generated for each site and consecutive subject numbers will be assigned to the random sequence (AR01 through ARXX and BR01 through BRXX). Screen failures will only have screening numbers assigned. Upon verification of inclusion and exclusion criteria each participant will be given the next unassigned consecutive subject number followed by their screening ID number as extension (for example, if the fourth person screened at Site A is the first person who meets all the study criteria their subject number would be AR01.004A.) Thus, each enrolled participant will have a unique subject number that identifies the site, the screening ID and the subject randomization and all participants who sign the informed consent document are accounted for in the subject disposition record.

5 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.

5.1 Interim Analysis

No interim analyses are planned. The double-blind random assignment will be secured by the sponsor until after study site data collection and database lock for the primary and exploratory endpoint data (FSFI scores and adverse events) are completed.

5.2 Deviations from the CIP

All deviations from the CI03 CIP will be recorded by study staff and assessed for potential impact on the primary outcome. Use of excluded concomitant medications, vaginal lubrication products, performance of oral sex prior to or during intercourse, and failure to attempt intercourse are considered protocol violations, with potential significant impact on FSFI-LD scores. Minor deviations include unavoidable out of window assessments and phone calls, ring use deviations, urine pregnancy tests conducted by mistake on participants who are not able to become pregnant and other events with little or no influence on the primary outcome. All deviations will be categorized and included (by treatment group) in a summary table for the final clinical study report.

6 STATISTICAL ANALYSES

The final Statistical Plan (SAP) will be completed prior to database lock and unblinding of the study data. Any deviations from the final analysis plan will be described and justified in the final clinical study report. Statistical analysis will be done using Minitab 19 Statistical Software (Minitab 2020).

6.1 Primary Efficacy Analysis

The planned primary efficacy analysis is a superiority comparison between the proportion of participants in each arm of the study who report FSFI-LD scores of 4.5 or better after using VR101 or the sham IVR for 4 weeks. This endpoint is assumed to reflect changes in FSFI-LD from baseline (Visit 1) to the study endpoint at Visit 2, 28 +/- 2 days later. The null hypothesis to be tested is that similar numbers of women in each of the study arms will report FSFI-LD scores of 4.5 or greater after 4 weeks of exposure to the study devices. The alternative hypothesis is that VR101 provides superior vaginal lubrication compared to the sham device. The planned test statistic is a simple test for the difference between two proportions, $\alpha = 0.05$, two-tailed test. Rejection of the null hypothesis will be interpreted as support for the alternative hypothesis, that there is a non-random superior effect on self-reported vaginal lubrication with use of the VR101 device compared to the sham device.

The primary efficacy analysis will use a normal approximation test with separate estimates of the true proportion of responders in each arm of the study to calculate a Z score

$$Z = \frac{(\hat{p}_1 - \hat{p}_2) - d_o}{\sqrt{\frac{\hat{p}_1(1-\hat{p}_1)}{n_1} + \frac{\hat{p}_2(1-\hat{p}_2)}{n_2}}}$$

where p_1 and p_2 are the observed proportions of responders in each group and the confidence interval for the difference between the two proportions is given by

$$\hat{p}_1 - \hat{p}_2 \pm z_{\alpha/2}\sqrt{\frac{\hat{p}_1(1-\hat{p}_1)}{n_1} + \frac{\hat{p}_2(1-\hat{p}_2)}{n_2}}$$

where $z_{\alpha/2}$ is the inverse cumulative probability of the standard normal distribution at $1 - \alpha/2$.

6.2 Exploratory Analyses

For exploratory analyses, mean total FSFI change from baseline will be compared across the study groups using a simple independent Student's *t*-test

$$t = \frac{(\bar{X}_1 - \bar{X}_2) - \delta_0}{s}$$

where equal variances are assumed

$$s = \sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}$$

and

$$DF = \frac{(VAR_1 + VAR_2)^2}{\frac{VAR_1^2}{n_{1-1}} + \frac{VAR_2^2}{n_2 - 1}}$$

a confidence interval for the difference between group means will be calculated,

$$(\overline{X}_1 - \overline{X}_2) - t_{\alpha/2}(S) \text{ to } (\overline{X}_1 - \overline{X}_2) + t_{\alpha/2}(S)$$

where $t_{\alpha/2}$ is the inverse cumulative probability of a t distribution at $1 - \alpha/2$, and effect size, Cohen's *d* is the standardized mean difference using the pooled standard deviation.

Independent Student's *t*-tests will also be calculated using group means for each of the FSFI domains. No adjustment for multiplicity is planned for the exploratory analyses. The broader population results of the exploratory analyses will be presented in tabular form.

7 ANALYSIS GROUPS

The target population for this study is the subset of women with deficient vaginal moisture/lubrication identified through inclusion and exclusion criteria and ability to independently place and remove an IVR. This is a subset of the broader population who would adhere to treatment with either the VR101 or sham IVR.

7.1 Full Analysis Set (ITT) and Modified ITT

The planned full analysis set includes all randomized participants. Because the ability to place and remove the study devices independently is not assessed until after randomization the primary efficacy analysis requires a modified ITT as it will not include participants who are unable to insert a vaginal ring. Subjects with other serious protocol violations will be assessed during the blind review for inclusion or exclusion in the final Modified ITT.

7.2 Complete Case Set

The subset of participants in the Modified ITT set who complete all study visits and for whom all outcome measures are collected.

7.3 Per Protocol Set

The subset of participants in the Modified ITT set who complied with the protocol sufficiently to ensure that data would be likely to represent the effects of the study treatments according to the underlying study model. Participants in this subset meet all inclusion and exclusion criteria, are able to place and remove an IVR independently, use the device as specified, complete both study visits and scheduled interim phone calls with no major protocol violations during 4 weeks of consecutive study device use. Anticipated major protocol violations include use of excluded concomitant medications, vaginal lubrication products, performance of oral sex prior to or during intercourse, and failure to attempt intercourse. Other protocol deviations will be assessed during the blind review of all collected data at the end of the study prior to unblinding. All protocol deviations will be classified as major or minor and will be tabulated for the clinical study report.

8 DISPOSITION OF MISSING DATA

8.1 Prevention of Missing Data

- Prevention of missing data is central to this study design. All participants will be counseled at enrollment on the importance of completing the study and communicating all issues and concerns to the study coordinator.

- Study staff will provide a “safe” place for disclosure of intent to withdraw from the study so that an Early Termination (ET) visit and final outcome measures can be collected prior to withdrawal of consent.

- If subject safety is assured, non-compliance with study requirements will not require early discontinuation.

- Case report forms will be designed to capture all relevant background information as well as objective reasons for early discontinuation when it cannot be prevented.

8.2 Incentive to Complete

- Under the FDA guidance for payment and reimbursement to research subjects, (January 2018) the sponsor will provide a study completion payment similar to the payment for one regular study visit for participants who complete the study per protocol with no missing data (also see final Informed Consent Form dated 31 January 2020).

- Participants who complete the 4-week double-blind study will be given the opportunity to continue in a 2-week open label extension where they will be guaranteed to receive the active VR101 device.

8.3 Unavoidable Loss of Data

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, enrollment in the study and randomization requires that all participants meet inclusion/exclusion criteria, including the Visit 1 FSFI-LD baseline. Initiation of treatment requires ability to independently place an IVR. The primary efficacy outcome, proportion of subjects who have a "functional" score of 4.5 or better after 4 weeks of treatment, is therefore dependent on a post randomization FSFI-LD score.

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 guidance documents, methods for handling missing data in this study will be determined by the reasons for "missingness" and predefined by updating the SAP after blind review. Appropriate sensitivity analyses will be specified to evaluate assumptions associated with handling of all missing data.

Where unavoidable, participants who successfully start but cannot complete 4 weeks of treatment will be scheduled for an Early Termination visit so the final (Visit 2) 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 discontinuation will be ascertained and recorded in the CRF. Prior to data lock and unblinding 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.

If final FSFI-LD are not available in excess of 5% of the unblinded data, mixed model regression that includes one or more auxiliary variables reflecting plausible assumptions around the uncertainty due to missing data will be conducted and subjected to sensitivity analysis.

8.4 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 and presented in a table for

the final study report. This information will also be used to determine whether additional sensitivity analyses are required during data analysis, and if so, the justification for these analyses and the outcomes will be included in the final report.

9 PLANNED SENSITIVITY ANALYSES

- An important assumption in this study is that the efficacy outcome, V2 FSFI-LD will distinguish the treatment arms at a "functional" score of 4.5 or better. The primary efficacy analysis is a comparison between proportions of subjects in each arm who reach this level of functionality. To test this assumption around the point estimate of functionality, a similar comparison between groups will be made for the proportion who report scores of 4.2 or better and the proportion who report scores of 4.8 or better.

- Robustness of the findings for point estimate proportions analysis will be assessed by conducting an area under the curve (AUC), Kaplan-Meier survival analysis using frequency data for percentages in each group achieving successively higher scores (4.2 through 6.0) on the Visit 2 FSFI-LD.

- The assumption that ability to place an IVR independently is not impacted by the assigned treatment arm (in other words, VR101 and the sham IVR are equally likely to result in instances of inability to place an IVR) will be tested by comparing the numbers of randomized subjects in each group who were not able to place the IVR, and repeating the primary efficacy analysis but including those subjects in the group denominators for the proportion comparison between groups.

10 POST STUDY BLIND DATA REVIEW

10.1 Final Data Validation

After all study procedures and data collection was completed and prior to breaking the randomization blind, the designated data review committee and study monitor reviewed case records to ascertain data quality and reliability, determine subject disposition, assignment to subgroups for data analyses, methods for dealing with missing data, and other relevant sensitivity analyses for alternate approaches to the data analyses.

10.2 Data Entry Verification

After the last participant completed the 1-week follow-up call after the open label phase of the study information from the study CRFs used in the blind review underwent double data-

entry and an independent data audit of database transfer was performed. All relevant data entry discrepancies and outstanding queries were resolved.

10.3 Data Quality and Reliability

The blind data quality and reliability review included an assessment of missing data, adherence to inclusion/exclusion criteria and screen fail rate, adherence to study visit and ring use schedules, study completion and early termination, demographics, medical history, intercourse history and intercourse record during the treatment phase of the study, use of concomitant medications, use of prohibited sources of vaginal lubrication, and other protocol deviations.

Relevant data were tabulated by site to examine potential site differences in the study population.

10.4 Blind Data Review Results

After careful review of the relevant data, Tables 1 through 5 were constructed for review. The data quality team found no missing data issues. Each of the randomized subjects who were able to place the IVR at Visit 1 provided final Visit 2 or ET efficacy data. Only one randomized subject, AR33, was unable to place the IVR and was terminated from study prior to providing any post randomization data.

Some trends toward demographic and baseline score differences were seen across the sites and it was determined that an exploratory analysis of site differences by treatment outcome would be added to the statistical analyses.

	VR101 Responders (%)	Sham IVR Responders (%)	*p*
Site 01			
Site 02			

As noted above, one randomized subject, AR33, was not able to place the IVR and was terminated from the study at Visit 1. The data review committee agreed that AR33 did not meet the requirements to be included in the target population (Section 8.2.1, CI03 Protocol) and would be excluded from the primary efficacy analysis.

One randomized subject, AR36, did not return for Visit 2 as scheduled and was initially reported to the sponsor as lost to follow-up. The site continued to attempt communication to avoid missing data and after 4 weeks discovered that the subject had developed pneumonia in the interim and had been too sick to respond or come in. By the time a final visit was scheduled, 4 weeks (30 days) had elapsed since she last used the study device. A review of the relevant FSFI literature in support for validity and reliability of FSFI recall beyond 1 week was negative and it was agreed that the Visit 2 data is too far out of the +/- 2 day window to be considered valid or reliable. Based on blind review, AR36 will be included in the modified ITT analysis as a nonresponder to provide a reliable estimate of VR101 efficacy.

One subject, AR26, reported an intercourse history of 270 events over the three months prior to screening. The median number of events for all other randomized subjects was found to be 12 and the mean was 19.3 with a minimum of 6 and a maximum of 90 (N = 174). In addition to being an extreme outlier regarding intercourse history, AR26 reported a Visit 1 FSFI lubrication score of 1.5 (out of 6, indicating major dysfunction), which appeared inconsistent with the reported intercourse history. During the treatment phase of the study her reported intercourse frequency dropped to 18 events per month, which was down from 90 events per month (270 events/three months) prior to entering the study. After rechecking the CRF data against source documents, no explanation or support for clinical authenticity of the subject's screening and inclusion data was found in the blind data review. The review committee agreed that AR26 will be included in the modified ITT analysis as a nonresponder to provide a reliable estimate of VR101 efficacy.

A comparison of the conclusions regarding VR101 efficacy between the randomized population and the modified ITT population will be performed and will allow for justification as to whether the modified ITT population as defined above leads to the same conclusions as the randomized population analysis.

Ring use variation and consistency was examined during the blind review and found to vary across the study population. This variance will be reviewed following unblinding and exploratory treatment by per protocol vs. non per protocol ring use analyses will be conducted. Results will be tabulated and included in the final clinical study report.

	VR101 Responders (%)	Sham IVR Responders (%)	*p*
Per Protocol Use			
Non Per Protocol Use			

10.5 Subject Assignment to Analysis Groups

For each randomized subject, a blind review of completion status, protocol deviations (major and minor), overall data quality and completeness was conducted. Subjects were evaluated for inclusion in the modified ITT primary efficacy analysis group and the per protocol efficacy analysis group. Early terminators (with complete data) were also identified for exploratory analysis by treatment group. Results of this review and blind assignment to analysis groups are shown in Table 5.

11 REFERENCES

Minitab 19 Statistical Software (2020). [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.

12 BLIND REVIEW SUMMARY TABLES

Table 1. Blind Review of Subject Completion, Protocol Deviations, and Analysis Subgroups by Site

	Site A (1)	Site B (2)	Total	Notes
Screened	116	105	221	
Screen Fail	26 (22.4%) Inc # 6 19 Inc # 5 1 Exc # 1 2 Exc # 5 1 Exc # 13 1 Exc # 13, 16 1 Inc # 4, Exc #1 1	19 (18.1%) Inc # 6 16 Inc # 5 1 Exc # 4 1 Inc # 4, Exc #1 1	45 (20.4%)	Expected screen fail was 30%
Randomized	90 (77.6%)	86 (81.9%)	176 (79.6%)	175 meet MITT criteria 1 Subject could not place ring so received no treatment and no post randomization measures were taken
Entered Treatment Phase	89	86	175	
Early Terminated	4 (4.5%)	5 (5.8%)	9 (5.1%)	ET final FSFI-LDs available for all.
Completed 4 weeks	85 (95.5%)	81 (94.2%)	166 (94.9%)	
Completed/ET with major protocol violations	6 (6.7%) Lube Use 4 Oral Sex 2	3 (3.5%) Lube Use 3	9 (5.1%)	
Completed/ET with other non-major protocol deviations	22 (24.7%)	33 (38.4%)	56 (32.0%)	
Completed/ET with no protocol violations recorded	61 (68.5%)	50 (58.1%)	110 (62.9%)	
Blind Review Data Quality Issues	2 (2.2%)	0 (0%)	2 (1.1%)	AR26 and AR 36

Table 2. Subject Demographics by Site

Menopausal status

	Site A	Site B	Total
Pre-Menopausal	32 (36.0%)	17 (19.8)	49 (28%)
Peri Menopausal	11 (12.4%)	5 (5.8%)	16 (9.1%)
Post-Menopausal	46 (51.7%)	64 (74.4%)	110 (62.9%)
Total	89 (100%)	86 (100%)	175 (100%)

Age of Participants at each site

Variable	Site ID	N	N*	Mean	StDev	Minimum	Median	Maximum
Age (years)	01	89	0	46.63	13.39	23.00	51.00	76.00
	02	86	0	52.12	11.71	21.00	56.00	74.00

*missing

Table 3 Visit 1 FSFI by Site

Visit 1 FSFI Distributions for each site

Variable	Site ID	N	N*	Mean	StDev	Minimum	Median	Maximum
Desire	01	90	0	3.440	1.236	1.200	3.600	6.000
	02	86	0	3.530	1.173	1.200	3.600	6.000
Arousal	01	90	0	3.713	1.227	1.200	3.600	6.000
	02	86	0	3.980	1.311	1.200	4.350	6.000
Lubrication	01	90	0	2.1700	0.7803	1.2000	2.2500	3.6000
	02	86	0	1.8628	0.7219	1.2000	1.5000	3.6000
Orgasm	01	90	0	3.107	1.393	1.200	3.200	6.000
	02	86	0	3.340	1.580	1.200	3.400	6.000
Satisfaction	01	90	0	3.756	1.175	1.200	3.600	6.000
	02	86	0	4.005	1.370	1.200	4.200	6.000
Pain	01	90	0	3.200	1.429	1.200	3.200	6.000
	02	86	0	2.633	1.264	1.200	2.400	6.000

Table 4. Visit 2 FSFI by Site

Visit 2 FSFI Distributions at each site

Variable	Site ID	N	N*	Mean	StDev	Minimum	Median	Maximum
Desire	01	89	0	3.728	1.191	1.200	3.600	6.000
	02	86	0	3.795	1.095	1.200	3.600	6.000
Arousal	01	89	0	4.325	1.179	1.200	4.500	6.000
	02	86	0	4.371	1.282	1.200	4.650	6.000
Lubrication	01	89	0	4.399	1.376	1.200	4.800	6.000
	02	86	0	4.190	1.687	1.200	4.800	6.000
Orgasm	01	89	0	4.144	1.583	1.200	4.400	6.000
	02	86	0	4.316	1.530	1.200	4.800	6.000
Satisfaction	01	89	0	4.733	1.011	2.400	4.800	6.000
	02	86	0	4.679	1.327	1.200	4.800	6.000
Pain	01	89	0	4.737	1.182	1.200	4.800	6.000
	02	86	0	4.340	1.729	0.000	4.800	6.000

*One subject, AR33, was unable to place the IVR after being randomized and was terminated at Visit 1 so did not provide Visit 2 FSFI data. Therefore, the N for Site 01 is reduced to 89 for the primary efficacy analysis.

Table 5. FSFI change from Baseline at Visit 2 by Site

Change in FSFI Domains at each site (FSFI1 – FSFI2)

Variable	Site ID	N	N*	Mean	StDev	Minimum	Median	Maximum
Desire change	01	89	0	0.283	1.028	-2.400	0.000	2.400
	02	86	0	0.265	0.990	-1.800	0.000	4.200
Arousal Change	01	89	0	0.610	1.382	-3.000	0.600	4.800
	02	86	0	0.391	1.220	-2.700	0.300	4.500
Lubrication Change	01	89	0	2.245	1.589	-1.800	2.400	4.800
	02	86	0	2.327	1.738	-1.200	2.400	4.800
Orgasm Change	01	89	0	1.052	1.863	-4.800	1.200	4.800
	02	86	0	0.977	1.692	-4.000	0.800	4.800
Satisfaction Change	01	89	0	0.989	1.370	-2.000	0.800	4.800
	02	86	0	0.674	1.511	-3.200	0.400	4.800
Pain Change	01	89	0	1.528	1.847	-3.600	1.600	4.800
	02	86	0	1.707	1.941	-6.000	2.000	4.800

Table 6. Blind Data Review: Subject Assignment to Analysis Groups

Subject Number	Randomized	Modified ITT (Efficacy Analysis)	Complete Case	W/out major Protocol Violations	Early Termination
AR01.001A	Yes	Yes	Yes	Yes	No
AR02.004A	Yes	Yes	Yes	Yes	No
AR03.002A	Yes	Yes	Yes	Yes	Yes
AR04.005A	Yes	Yes	Yes	Yes	No
AR05.008A	Yes	Yes	Yes	Yes	No
AR06.011A	Yes	Yes	Yes	Yes	No
AR07.010A	Yes	Yes	Yes	Yes	No
AR08.012A	Yes	Yes	Yes	Yes	No
AR09.009A	Yes	Yes	Yes	Yes	No
AR10.015A	Yes	Yes	Yes	Yes	No
AR11.013A	Yes	Yes	Yes	Yes	No
AR12.016A	Yes	Yes	Yes	Yes	No
AR13.018A	Yes	Yes	Yes	Yes	No
AR14.020A	Yes	Yes	Yes	Yes	No
AR15.021A	Yes	Yes	Yes	Yes	No
AR16.024A	Yes	Yes	Yes	Yes	No
AR17.023A	Yes	Yes	Yes	No	No
AR18.026A	Yes	Yes	Yes	Yes	No
AR19.028A	Yes	Yes	Yes	Yes	No
AR20.029A	Yes	Yes	Yes	Yes	No
AR21.030A	Yes	Yes	Yes	Yes	No
AR22.031A	Yes	Yes	Yes	Yes	No
AR23.033A	Yes	Yes	Yes	Yes	No
AR24.034A	Yes	Yes	Yes	Yes	No
AR25.035A	Yes	Yes	Yes	Yes	No
AR26.037A	Yes	Yes*	Yes	No*	No
AR27.036A	Yes	Yes	Yes	Yes	No
AR28.038A	Yes	Yes	Yes	Yes	No
AR29.039A	Yes	Yes	Yes	Yes	No
AR30.040A	Yes	Yes	Yes	Yes	No
AR31.042A	Yes	Yes	Yes	Yes	No
AR32.043A	Yes	Yes	Yes	Yes	No

Subject Number	Randomized	Modified ITT	Complete Case	W/out major Protocol Violations	Early Termination
AR33.044A	Yes	NA	NA	NA	NA
AR34.045A	Yes	Yes	Yes	No	No
AR35.046A	Yes	Yes	Yes	Yes	No
AR36.048A	Yes	Yes**	Yes	No**	No
AR37.047A	Yes	Yes	Yes	Yes	No
AR38.049A	Yes	Yes	Yes	Yes	No
AR39.050A	Yes	Yes	Yes	Yes	No
AR40.052A	Yes	Yes	Yes	Yes	No
AR41.051A	Yes	Yes	Yes	Yes	No
AR42.053A	Yes	Yes	Yes	Yes	No
AR43.055A	Yes	Yes	Yes	Yes	No
AR44.054A	Yes	Yes	Yes	Yes	No
AR45.056A	Yes	Yes	Yes	Yes	No
AR46.057A	Yes	Yes	Yes	Yes	No
AR47.058A	Yes	Yes	Yes	Yes	No
AR48.060A	Yes	Yes	Yes	Yes	No
AR49.063A	Yes	Yes	Yes	Yes	No
AR50.061A	Yes	Yes	Yes	Yes	No
AR51.062A	Yes	Yes	Yes	Yes	No
AR52.064A	Yes	Yes	Yes	Yes	No
AR53.065A	Yes	Yes	Yes	Yes	No
AR54.066A	Yes	Yes	Yes	Yes	No
AR55.068A	Yes	Yes	Yes	Yes	No
AR56.069A	Yes	Yes	Yes	Yes	No
AR57.071A	Yes	Yes	Yes	Yes	No
AR58.070A	Yes	Yes	Yes	Yes	No
AR59.072A	Yes	Yes	Yes	Yes	No
AR60.073A	Yes	Yes	Yes	Yes	No
AR61.074A	Yes	Yes	Yes	Yes	No
AR62.076A	Yes	Yes	Yes	No	No
AR63.077A	Yes	Yes	Yes	Yes	No
AR64.078A	Yes	Yes	Yes	Yes	No
AR65.079A	Yes	Yes	Yes	Yes	No
AR66.083A	Yes	Yes	Yes	Yes	Yes
AR67.084A	Yes	Yes	Yes	Yes	No
AR68.087A	Yes	Yes	Yes	No	No

Subject Number	Randomized	Modified ITT	Complete Case	W/out major Protocol Violations	Early Termination
AR69.088A	Yes	Yes	Yes	Yes	No
AR70.089A	Yes	Yes	Yes	Yes	Yes
AR71.091A	Yes	Yes	Yes	Yes	No
AR72.092A	Yes	Yes	Yes	Yes	No
AR73.094A	Yes	Yes	Yes	Yes	No
AR74.095A	Yes	Yes	Yes	Yes	No
AR75.096A	Yes	Yes	Yes	Yes	No
AR76.097A	Yes	Yes	Yes	No	Yes
AR77.099A	Yes	Yes	Yes	Yes	No
AR78.100A	Yes	Yes	Yes	Yes	No
AR79.101A	Yes	Yes	Yes	No	No
AR80.102A	Yes	Yes	Yes	Yes	No
AR81.103A	Yes	Yes	Yes	Yes	No
AR82.104A	Yes	Yes	Yes	Yes	No
AR83.105A	Yes	Yes	Yes	Yes	No
AR84.106A	Yes	Yes	Yes	Yes	No
AR85.107A	Yes	Yes	Yes	Yes	No
AR86.108A	Yes	Yes	Yes	Yes	No
AR87.109A	Yes	Yes	Yes	Yes	No
AR88.113A	Yes	Yes	Yes	Yes	No
AR89.114A	Yes	Yes	Yes	Yes	No
AR90.116A	Yes	Yes	Yes	Yes	No
BR01.001B	Yes	Yes	Yes	Yes	No
BR02.002B	Yes	Yes	Yes	Yes	No
BR03.003B	Yes	Yes	Yes	Yes	No
BR04.005B	Yes	Yes	Yes	Yes	No
BR05.006B	Yes	Yes	Yes	Yes	No
BR06.004B	Yes	Yes	Yes	Yes	No
BR07.007B	Yes	Yes	Yes	Yes	No
BR08.009B	Yes	Yes	Yes	Yes	No
BR09.008B	Yes	Yes	Yes	Yes	No
BR10.010B	Yes	Yes	Yes	Yes	No
BR11.011B	Yes	Yes	Yes	Yes	No
BR12.012B	Yes	Yes	Yes	Yes	No
BR13.013B	Yes	Yes	Yes	Yes	No
BR14.015B	Yes	Yes	Yes	Yes	No

Subject Number	Randomized	Modified ITT	Complete Case	W/out major Protocol Violations	Early Termination
BR15.018B	Yes	Yes	Yes	Yes	No
BR16.017B	Yes	Yes	Yes	Yes	No
BR17.016B	Yes	Yes	Yes	Yes	No
BR18.020B	Yes	Yes	Yes	Yes	No
BR19.019B	Yes	Yes	Yes	Yes	No
BR20.022B	Yes	Yes	Yes	Yes	No
BR21.021B	Yes	Yes	Yes	Yes	Yes
BR22.023B	Yes	Yes	Yes	Yes	No
BR23.026B	Yes	Yes	Yes	Yes	No
BR24.025B	Yes	Yes	Yes	Yes	No
BR25.027B	Yes	Yes	Yes	Yes	No
BR26.028B	Yes	Yes	Yes	Yes	No
BR27.029B	Yes	Yes	Yes	Yes	No
BR28.031B	Yes	Yes	Yes	No	No
BR29.032B	Yes	Yes	Yes	Yes	No
BR30.033B	Yes	Yes	Yes	Yes	Yes
BR31.035B	Yes	Yes	Yes	Yes	No
BR32.034B	Yes	Yes	Yes	Yes	No
BR33.036B	Yes	Yes	Yes	Yes	No
BR34.037B	Yes	Yes	Yes	Yes	No
BR35.039B	Yes	Yes	Yes	Yes	No
BR36.040B	Yes	Yes	Yes	Yes	No
BR37.041B	Yes	Yes	Yes	Yes	No
BR38.042B	Yes	Yes	Yes	Yes	No
BR39.044B	Yes	Yes	Yes	Yes	No
BR40.045B	Yes	Yes	Yes	Yes	No
BR41.046B	Yes	Yes	Yes	Yes	No
BR42.047B	Yes	Yes	Yes	Yes	No
BR43.048B	Yes	Yes	Yes	Yes	No
BR44.049B	Yes	Yes	Yes	Yes	No
BR45.051B	Yes	Yes	Yes	Yes	No
BR46.052B	Yes	Yes	Yes	Yes	No
BR47.053B	Yes	Yes	Yes	Yes	No
BR48.054B	Yes	Yes	Yes	Yes	No
BR49.057B	Yes	Yes	Yes	Yes	No
BR50.058B	Yes	Yes	Yes	Yes	No

Subject Number	Randomized	Modified ITT	Complete Case	W/out major Protocol Violations	Early Termination
BR51.059B	Yes	Yes	Yes	Yes	No
BR52.060B	Yes	Yes	Yes	Yes	No
BR53.062B	Yes	Yes	Yes	Yes	No
BR54.063B	Yes	Yes	Yes	Yes	No
BR55.064B	Yes	Yes	Yes	Yes	No
BR56.068B	Yes	Yes	Yes	Yes	No
BR57.070B	Yes	Yes	Yes	Yes	No
BR58.071B	Yes	Yes	Yes	Yes	No
BR59.072B	Yes	Yes	Yes	Yes	No
BR60.074B	Yes	Yes	Yes	Yes	No
BR61.077B	Yes	Yes	Yes	Yes	No
BR62.079B	Yes	Yes	Yes	Yes	No
BR63.078B	Yes	Yes	Yes	Yes	No
BR64.081B	Yes	Yes	Yes	Yes	No
BR65.080B	Yes	Yes	Yes	Yes	No
BR66.082B	Yes	Yes	Yes	No	Yes
BR67.083B	Yes	Yes	Yes	Yes	No
BR68.084B	Yes	Yes	Yes	Yes	No
BR69.085B	Yes	Yes	Yes	Yes	No
BR70.086B	Yes	Yes	Yes	Yes	No
BR71.087B	Yes	Yes	Yes	Yes	No
BR72.089B	Yes	Yes	Yes	Yes	No
BR73.090B	Yes	Yes	Yes	Yes	Yes
BR74.092B	Yes	Yes	Yes	No	Yes
BR75.093B	Yes	Yes	Yes	Yes	No
BR76.095B	Yes	Yes	Yes	Yes	No
BR77.094B	Yes	Yes	Yes	Yes	No
BR78.096B	Yes	Yes	Yes	Yes	No
BR79.097B	Yes	Yes	Yes	Yes	No
BR80.099B	Yes	Yes	Yes	Yes	No
BR81.100B	Yes	Yes	Yes	Yes	No
BR82.101B	Yes	Yes	Yes	Yes	No
BR83.102B	Yes	Yes	Yes	Yes	No
BR84.103B	Yes	Yes	Yes	Yes	No
BR85.104B	Yes	Yes	Yes	Yes	No
BR86.105B	Yes	Yes	Yes	Yes	No

*AR26 will be included in the modified ITT analysis as a nonresponder to provide a reliable estimate of VR101 efficacy. She will not appear in the per protocol group.

**AR36 will be included in the modified ITT analysis as a nonresponder to provide a reliable estimate of VR101 efficacy. She will not appear in the per protocol group.