Title: TP-00002 Rinovum Subsidiary 2, LLC: Disposable Stress Urinary Incontinence Pessary Device Efficacy and Safety Study

Protocol Identifying Number: <TBD>

Principal Investigator: < Principal investigator>

Sponsor: Rinovum Subsidiary 2, LLC.

Funded by: Rinovum Subsidiary 2, LLC.

Version Number: v3.0 2017 November 03

References:

- 21 CFR Part 812 Investigational Device Exemptions
- 21 CFR Part 50 Protection of Human Subjects; Informed
- 21 CFR Part 54 Financial Disclosure by Clinical Investigators
- 21 CFR Part 56 Institutional Review Boards
- 45 CFR Part 46 Protection of Human Subjects
- United States Food and Drug Administration (FDA), Medical Device Clinical Study Guidance
- Guidance for Industry and Food and Drug Administration Staff: Clinical Investigations for the Treatment of Urinary Incontinence

LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOV	Analysis of Covariance
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Science
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CMS	Centers for Medicare and Medicaid Services
CRF	Case Report Form
CRO	Contract Research Organization
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICH E6	International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Investigational Review Board
ISO	International Organization for Standardization
LSMEA	Least-squares Means
MedDR	Medical Dictionary for Regulatory Activities
MCID	Minimal Clinical Important Difference
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NIH	National Institutes of Health
NIH IC	NIH Institute & Center
OHRP	Office for Human Research Protections
OTC	Over the Counter
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

STATEMENT OF COMPLIANCE

This clinical trial will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 812)
- ICH E6

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training.]

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: Print/Type Name

Signed: Date: _____

PROTOCOL SUMMARY

Title: Rinovum Subsidiary 2, LLC. Disposable Stress Urinary Incontinence Device Efficacy and Safety Study

Précis: This study is an interventional, single arm, multi-center study. It will be conducted at sites in the northeastern United States. The protocol will be approved by Chesapeake IRB or applicable local IRBs. The sample size will consist of approximately 50 participants. Participants will undergo an initial control period in which preweighed pads will be worn for 7 consecutive days for 12 hours. This will be followed by device usage for 14 consecutive days where participants will wear both device and preweighed pads simultaneously. for 12 hours.

Objectives: The purpose of this study is to evaluate the efficacy and safety of an over-the-counter (OTC) disposable stress urinary incontinence (SUI) pessary device. Specifically, this study will evaluate the effectiveness of the pessary device by assessing reduction in urine leakage in approximately 50 women with Stress Urinary Incontinence (SUI). Efficacy will be assessed by mean pad weight gain per hour, reduction of stress urinary incontinence events per day, and a quality of life questionnaire. The safety of the OTC SUI pessary device will be evaluated by assessing all adverse events, including the results of urinalysis, vaginal swab, and vaginal examination.

Primary Objective: Demonstrate effectiveness of device usage

Important Secondary Objectives: Device reduces episodes of incontinence, improves quality of life, and is safe for over-the-counter (OTC) use.

Endpoints:

Primary Endpoint: Mean pad weight gain reduction per hour is >50% during the last 7 days of the treatment phase as compared to the baseline phase.

Important Secondary Endpoints:

(1) Reduction in mean number of SUI episodes per day from the 7-day baseline period to the last 7 days of the 14-day device treatment period. Participants will record SUI episodes in the Study Diary during the baseline (7 days) and treatment (14 days) periods. Negative values are indicative of efficacious outcome.

(2) Change in Quality of Life as Measured by the ICIQ-LUTSqol Quality of Life Questionnaire.

The Quality of Life Questionnaire to be performed at baseline, before, and after treatment phase of the study is based on 20 questions referring to areas which may have been influenced or changed by accidental urine loss and/or prolapse. These questions are assigned a value of, 1 = 'Not at all,' 2= 'Slightly,' 3 = 'Moderately,' or 4 'A lot.' Each area is then assessed on a scale of 1-10 to see how much it bothers them. The Questionnaire is scored by taking the average score of items and then multiplying that value by 25 to put scores on a scale from 0 to 100. A lower score is considered less impact to quality of life and a higher score reflects more impact to quality of life. In the same manner, a reduction in scores from baseline reflects improved quality of life. A reduction in

score of ≥ 3.7 is considered the Minimum Clinically Important Difference (MCID).

(3) Evaluation of Adverse Event assessments to determine device is safe for use.

Important Exploratory Endpoints:

(1) Participants can successfully use the device in accordance with the given Instructions for Use.

(2) Participants will find the device comfortable enough to demonstrate compliance with the study procedures during the device treatment phase.

Population: Approximately 50 female participants over the age of 18 who have been physician diagnosed with Stress Urinary Incontinence; have a normal voiding history; are familiar with the use of tampons; and have had a Normal Pap Smear <36 months prior to study enrollment.

Phase: Efficacy and Safety

Number of Sites enrolling participants: 4

Description of Study Agent: A disposable stress urinary incontinence pessary device worn daily for 12 hours.

Endpoint Classification:	Efficacy and Safety Study
Interventional Model:	Single Group, Open Study
Masking:	Open Label
Primary Purpose:	Efficacy and Safety

Study Duration: 6-12 months

Participant Duration: 2 months

SCHEMATIC OF STUDY DESIGN

Prior to Enrollment (Screening)

Total N: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain and document medical history. Confirm that participant symptoms indicate SUI diagnosis. Perform the urine pregnancy test (if applicable), urinalysis, vaginal examination and symptom evaluation to ensure participant has no active urinary or vaginal infection requiring treatment. A vaginal swab will be performed to establish baseline vaginal microflora. Perform usability and fit assessment test.

NOTE: Results of the SUI diagnosis assessment and fit assessment may deem participant ineligible for enrollment due to urge incontinence or mixed (stress and urge) incontinence diagnosis or poor /improper fit. To simulate OTC use, participants will be asked to perform self-selection and assess fit based on the product labeling prior to confirmation by the PI.

Enrollment/Visit 1 Time Point

Total N: Complete a questionnaire by the physician. Participant will also complete a baseline Quality of Life Questionnaire.

Participant will receive 14 preweighed pads to take home. Participant will perform control phase of study wearing pads for 12 hours/day for 7 consecutive days. Pads will be returned by participant for weighing and data collection.

NOTE: Results of the laboratory tests from the screening visit (pregnancy test, vaginal examination and urinalysis test) may deem a participant ineligible for enrollment due to positive pregnancy result, positive vaginal infection requiring treatment, or positive urinary infection requiring treatment, respectively.

Visit 2 Time Point

Total N: Urine pregnancy test, if applicable, to rule out pregnancy, vaginal examination, and symptom evaluation will be repeated to rule out any potential infection requiring treatment. Vaginal swab will also be repeated to evaluate changes in vaginal microflora. Quality of Life questionnaire will be repeated. Participants will be given 20 study devices and 28 preweighed pads to perform the treatment phase of the study. Participants will wear 14 devices and 14 pads simultaneously for 14 consecutive days. Pads will be returned by participant for weighing and data collection, and participants will record information regarding activity level and quality of life.

Visit 3 Time Point

Total N: Examination to determine final safety evaluation via investigator vaginal examination, vaginal swab, urinalysis, study questionnaire to collect final comments on device usage, and repeat Quality of Life questionnaire to evaluate changes in quality of life post treatment with device

Note (1): For pre-menopausal women, and women who have not undergone a hysterectomy, a Urine Pregnancy Test, usually to be done within 24 hours prior to study intervention is required. Results must be available prior to administration of study product, unless otherwise indicated by the physician.

1 KEY ROLES

Sponsor	Stephen Bollinger, President Rinovum Subsidiary 2, LLC. 300 Oxford Drive Suite 330 Monroeville, PA 15146 412-200-7996 sbollinger@rinovum.com
Principal Investigator	<Insert text>
Sub Investigator	<Insert text>
Study Coordinator	<Insert text>
Clinical Laboratory	<Insert text>
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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Stress urinary incontinence (SUI) occurs predominantly among women. SUI is characterized by loss of urine resulting from increased abdominal pressures that occur when coughing, laughing, sneezing, running, lifting or walking. SUI causes quality of life degradation and contributes to women refraining from maintaining normal physical activities, and is also associated with low libido, vaginal dryness, dyspareunia.

Currently, there are several types of treatment options for SUI such as:

- Lifestyle/Behavioral changes including weight loss, pelvic floor strengthening exercises (Kegel), biofeedback, dietary changes and advisement to decrease fluid intake have been shown to have good results for motivated patients. However, it is difficult to compliance is relatively low.
- Non-surgical treatments, including Absorbent Pads; Pessary support devices (originally intended to support bladder prolapse) which elevate the vesico-urethral angle, devices that provide urethral occlusion, and weighted cones.
- Pharmacologic Therapy
- Surgical methods, including retropubic urethropexies, suburethral slings and periurethral injection of bovine collagen or carbon-coated beads.[1]

Relevant clinical research demonstrates a need for nonsurgical options for treating SUI. Since the aging populations is growing, there are more instances of incontinence. Conservative treatment is fundamental as it is the only type of care many patients need or can undergo.[2]

[1]Mark Deutchman, Meghan Wulster-Radcliffe. Stress Urinary Incontinence in Women: Diagnosis and Medical Management, 2005.
[2] Metcalf, et al. The Non-surgical Options for SUI – Is Any One Optimal?, 2016

Approximately 25% of premenopausal and 40% of postmenopausal women suffer from urinary incontinence, with the peak incidence beginning at around age 45-49. Of those dealing with urinary incontinence, 51% have stress urinary incontinence. Women that are Caucasian, have a BMI $\geq$ 30 kg/m^2, have been pregnant, and have had a vaginal delivery are at a higher risk of developing SUI. Intrinsic factors contributing to development of SUI include urethral musculature, blood flow and innervation. Extrinsic factors include degree of urethral support, patient weight, and degree of physical activity.

Multiple treatment methods have been studied, including surgery, pharmacological treatments, physical/behavioral therapy, and non-surgical options such as pessaries and intravaginal devices. While multiple treatment options exist, less than a third of women seek intervention in the first 12 months of experiencing SUI symptoms.

Surgical interventions have existed for over 100 years and are regarded as the most effective and durable treatment option for urinary incontinence; however, this surgery comes with physiological risks to the patient, high hospital costs, and productivity loss during recovery. While pharmacological options exist, they are not the standard of care in urinary incontinence treatment in the United States. While some topical pharmacologic are proven to resolve incontinence in some women, studies have shown both adrenergic drugs and oral hormonal treatments ineffective. One study revealed an 80% increase in incontinence in post-menopausal women. Not only have studies shown pharmacological treatments ineffective, they also carry side effects such as nausea, dry mouth, and fatigue. Having nonsurgical treatments are vital so that patients have reversible, safer, and less costly options to try before resorting to surgical and pharmacological treatments.

The primary nonsurgical and nonpharmacological options include behavioral and physical therapy, pessaries, and disposable, intravaginal devices, which are all relatively low risk and low cost. Pelvic floor muscle training combined with bladder training is effective; however, it is difficult for patients to comply with this treatment regimen and requires more extensive physician guidance. Understanding predictors of success will aid in patient counseling on treatment options. Menopausal status, education level, UI surgery status, and incontinence frequency were consistently identified as predictors of success across those that used behavioral therapy, pessaries, and a combination of both. Women that were post-menopausal, had higher education, no previous UI surgery, and had low incontinence frequency were found to have the most success when using nonsurgical treatments.

A study comparing cost utility of different treatment options revealed that incontinence pessaries were the most cost effective. Pessaries have been found to increase continence by 64-75%. While 50-75% of women decline pessaries when recommended, over three quarters of patients that use the pessary continue to use after one year. Studies have also revealed that women do not perceive any difference in the effectiveness of pessary treatment versus physical therapy treatment; however, pessary use is also associated with pain, irritation, UTIs and difficulty in physician fitting of the pessary.

A study performed to evaluate the efficacy and safety of a novel disposable intravaginal device for the treatment of SUI was performed at 2 sites in Israel. Sixty women were recruited and enrolled into the study and used the device for 28 – days after a 7-day control period. During the control period, preweighed pads were worn daily for 8 hours to determine a baseline for participants. This period was followed by a 28-day usage period. The last 14 days of the control period were used to allow for participants to find the right size device. The primary endpoint was

the percentage of women who achieved a ≥ 70% reduction in pad weight gain (PWG) from the control period to the last 14 days of device usage. The results demonstrated that 85% of participants met the success criteria. The device was concluded to be easy to use, well-tolerated, and effective in reducing SUI[3].

As is recommended in the Guidance for Industry and FDA Staff: Clinical Investigations of Devices Indicated for the Treatment of Urinary Incontinence, the Rinovum Subsidiary 2, LLC. SUI Device Pivotal Study will include the use of a voiding diary to document leakage occurrence daily. Also, as recommended in the guidance, the study will use pad-weighing to monitor efficacy of the device. The 24-hour test parameter will be used, but will be tailored to be in line with the amount of time the device will be used for treatment each day (12 hours). Participants will be provided with ziplock bags and mailers so that used pads can be collected daily and weighed by the site clinical team within 48 hours to determine the amount of pad weight gain (PWG). Note that more than 1 pad may be worn throughout each day depending on the amount of leakage protection required.

2.2 RATIONALE

This study is an interventional, open label, single-arm, clinical study in which participants will serve as their own controls. This study will enroll participants deemed eligible per the Inclusion/Exclusion Criteria. This study will evaluate the safety and effectiveness of the Rinovum Subsidiary 2 (RS-2) SUI pessary device by assessing reduction in urine leakage in approximately 50 women with SUI. Efficacy will be assessed by reduction in pad weight gain, frequency of stress urinary incontinence events, and a quality of life questionnaire. The study design consists of a control/no treatment period for each subject and a device treatment period for each subject.

The participants in this study will use the pre-weighed pads daily for 12 hours per day to obtain baseline control urine leakage data. This baseline will be for 7 consecutive days. The pads may be changed as necessary during this time. The same participants will use the device, and the same pre-weighed pad method for 14 consecutive days during the treatment period. Participants will be asked to schedule the treatment phase during a time when they will not have an interruption in the treatment phase such as menstrual cycle or travel. Patients will be asked to perform the treatment period within 21 days. In both the non-treatment and treatment phase of the study, the preweighed pads will be collected and weighed for use in calculating pad weight gain (PWG).

Safety analysis will include results of urinalysis, vaginal swab, vaginal examination, and evaluation of adverse events.

Usability of the device will be assessed by the PI at Enrollment where the participant will insert the device while following the Instructions for Use. The PI will examine the device inside the vagina to ensure successful placement and fit.

2.3 POTENTIAL RISKS AND BENEFITS

The risk profile of the Rinovum Subsidiary 2 SUI device is considered to be low. Risks to participants in this study are comparable to those routinely encountered with using vaginal

[3] Ziv E, Stanton SL, Abarbenel J. Efficacy and safety of a novel disposable intravaginal device for treating stress urinary incontinence. Am J Obstet Gynocol 2008; 198:594.e1 – 594.e7.

pessaries. The study presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context with a Class II device.

Potential risks include the following short-term risks:

- Sensitivity to the materials used in the device; however, the probability is low due to the design specification.
- Injury if the user does not understand the instructions for use. Prior to the pivotal study, label comprehension and simulated use testing will occur to refine the labelling and demonstrate safety to proceed with the pivotal study
- Irritation to the vaginal area
- Vaginal bleeding/spotting
- Urinary Tract Infection (UTI)
- Vaginal infection
- Urine Retention
- Infection if the device is not used as indicated. For example, reuse of the device could put the user at risk of infection. Instructions for use will include details regarding single, disposable use of the device and the specifications will preclude reuse by design.
- Confidentiality

There are no known long-term risks associated with this study.

This study is a non-significant risk study. The device is not intended as an implant or for use in supporting or sustaining human life. The device is intended to treat by assisting with management of the symptoms associated with a disease (Stress Urinary Incontinence). Due to the low risk profile associated with the Rinovum Subsidiary 2 SUI device, as well as other similar devices, it does not present serious risk to the health, safety, or welfare of a subject.

The materials used in the manufacturing of this device are medical-grade. During the screening process, a pregnancy test, vaginal examination and urinalysis will be performed to rule out a pregnancy, vaginal infection, or UTI, respectively. The device will be tested the screening visit to ensure fit, comfort and ability to urinate while wearing the device. A vaginal swab will be collected to establish baseline vaginal microflora, but will not be used for determining eligibility to enroll. Participants' most recent Pap smear within 36 months must be normal. Each of the participants will receive an identification number during enrollment. This number will be the only identifying factor on the CRF/questionnaire. The PI will maintain the participant information in a secure location. The Sponsor shall have access to the study data after it has been de-identified to analyze the data to determine success of the study.

Each of the devices used in this study will be labeled "Caution: Investigational device. Limited by United States law to investigational use". Additionally, each device will have a specific lot number.

Patient's undergoing successful intravaginal pessary treatment for SUI have been shown to have improvement in quality of life, so long as the device is being used. The quality of life improvement seen in patients undergoing successful SUI treatment include physical mitigation of symptoms which result in potential social effects, psychological effects and decrease in activity.

Non-surgical treatment options are important to the subject population. SUI device interventions that demonstrate efficacy and safety could significantly improve the quality of life for a condition that most patients do not like to discuss, even with their physicians. Surgical options are typically used as a last resort, so the RS-2 SUI pessary device could provide a bridge to surgery option for

patients. For this reason, the potential benefits associated with this study outweigh the risks involved.

The potential benefits to participants during this study include increased quality of life, increased social activity (including exercise), psychological improvement, and increased confidence due to decreased urinary leakage.

3 OBJECTIVES AND PURPOSE

This study is an interventional, open label, clinical study. The purpose of this study is to evaluate the efficacy and safety of the Rinovum Subsidiary 2, LLC disposable SUI pessary device. Specifically, this study will evaluate the effectiveness of the pessary device by assessing reduction in urine leakage in approximately 50 women with Stress Urinary Incontinence (SUI). Efficacy will be assessed by the reduction in mean pad weight gain per hour, reduction in the mean number of stress urinary incontinence events per day, and a quality of life questionnaire. Primary Objective is to demonstrate effectiveness of device usage. Important Secondary Objectives include demonstrating that the device reduces episodes of incontinence, improves quality of life, and is safe for over-the-counter (OTC) use. The safety will be evaluated by assessing all adverse events, including the results of urinalysis, vaginal swab, and vaginal examination.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

60 to 70 women having diagnosed stress urinary incontinence (SUI) will be recruited from multiple study sites and the general population, while approximately 50 women will be included in the Per Protocol population. The participants will wear preweighed pads for 7 consecutive days during the non-treatment (control) phase. Participants will then use the device for 14 consecutive days during the treatment phase. During enrollment, before treatment phase and after treatment phase, a vaginal swab will be collected to determine any changes in the vaginal microflora of the participant.

4.2 ANALYSIS POPULATIONS

Intent to Treat Population (ITT): Any subject enrolled who gets a pre-weighed pad for the control phase. This is expected to be 60-70 subjects.

Modified Intent to Treat Population (mITT): Any subject enrolled who gets through the control phase, is given the device and pads for the treatment period, and who uses the device such that there is at least one data point to analyze - i.e., use of the pad for at least one hour during the last 7 days of the treatment period. A subject who is not in the study at the beginning of the last 7 days of the treatment period is in the ITT population but not the mITT population. The mITT is the population the analysis will be done on.

Per Protocol Population (PP): Any subject getting through the entire treatment period and has complete data (i.e., pad weight reduction data for the last 7 days of the treatment period). For example, someone having only data for 6 out of the last 7 days of the treatment period is in the mITT population but not the PP population.

Safety Population (SP): Same as ITT.

4.3 STUDY ENDPOINTS

The primary endpoint is the percentage reduction in mean pad weight gain per hour of >50% during the 14-day treatment phase versus the 7-day baseline phase. The PWG percentage reduction will be calculated by comparing the mean PWG over the 7-day baseline non-treatment phase with the last 7 days of the 14-day treatment phase for each individual participant.

Important secondary endpoints will be measured based on anecdotal evidence or feedback from the subjects. These secondary endpoints are as follows:

(1) Reduction in mean number of SUI episodes per day from episodes from the 7-day baseline period to the last 7 days of the 14-day device treatment period as measured as reduction (improvement) in stress urinary incontinence episodes. Participants will record SUI episodes in the Study Diary during the baseline (7 days) and treatment (14 days). Negative values are indicative of efficacious outcome.

(2) Change in Quality of Life as Measured by the ICIQ-LUTSqol Quality of Life Questionnaire.

The Quality of Life Questionnaire to be performed at baseline, before and after treatment phase of the study is based on 20 questions referring to areas which may have been influenced or changed by accidental urine loss and/or prolapse. These questions are assigned a value of, 1 = 'Not at all,' 2= 'Slightly,' 3 = 'Moderately,' or 4 'A lot.' Each area of changed is then assessed on a scale of 1-10 to see how much it bothers them. The Questionnaire is scored by taking the average score of items and then multiplying the average by 25 to put scores on a scale from 0 to 100. A lower score is considered less impact to quality of life and a higher score reflects more impact to quality of life. In the same manner, a reduction in scores from baseline reflects improved quality of life. A reduction on score of $\geq$ 3.7 is considered the Minimum Clinically Important Difference.

(3) Evaluation of Adverse Event assessments to determine device is safe for use.

Important Exploratory Endpoints are as follows:

(1) Participants can successfully use the device in accordance with the given Instructions for Use.

(2) Participants will find the device comfortable enough to demonstrate compliance with the study procedures during the device treatment phase.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

Inclusion Criteria: To be eligible to participate in this study, an individual must meet all of the following criteria:

- Provision of signed and dated informed consent form
- Literacy must be in English (able to read and understand Informed Consent)
- Stated willingness to comply with all study procedures and availability for the duration of the study
- Female, aged >18

- Be in generally good heath as determined by the Investigator
- Have a physician diagnosis of SUI that occurred prior to or during the screening visit of this study
- Have a ≥ 3-month history of experiencing > 3 episodes of SUI per week
- Be willing to use the investigational pessary device for the control of urinary incontinence
- Have experience with wearing a tampon
- Have normal PAP smear results within the last 36 months, if applicable.

5.2 PARTICIPANT EXCLUSION CRITERIA

Exclusion Criteria: An individual who meets any of the following criteria will be excluded from participation in this study:

- Is pregnant, or planning to become pregnant during the study
- Has been physician diagnosed with urge urinary incontinence or mixed urinary incontinence prior to or during the screening visit for this study
- Is post-partum within 3 months
- Has had an intrauterine device (IUD) placement of less than 6 months
- Has self-reported difficulty emptying her bladder;
- Has a history of Toxic Shock Syndrome (TSS) or symptoms consistent with TSS;
- Has experienced difficulty inserting or wearing an intra-vaginal device, including a tampon;
- Has had vaginal surgery, perineal surgery, uterine surgery, or abortion (spontaneous or induced) within the past 3 months;
- Has any Screening laboratory value outside the laboratory reference range considered clinically significant by the Investigator which could impact the safety of the participant or the outcome of the study
- Has an active urinary tract infection or vaginal infection requiring treatment
- If for any reason, the Investigator decides that the participant should not participate in the study.
- Class III Obesity (BMI≥ 40.0 kg/m^2)
- Advanced prolapse
- Fit assessment is not successful during screening visit

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Study participants will be recruited with the use of an advertisement flyer to be posted locally and online. They will also be recruited by the primary investigators patient pool and general public. Any interested potential participants will contact the Primary Investigator or Study Coordinator. The participants will be informed that participation is voluntary and the decision to participate or not, will in no way affect their future care. Subsequently, the participants will be given a complete and thorough explanation of the benefits and risks or discomforts that may be anticipated with this study.

Participants will be given a monetary compensation for time and transportation in the amount of $550.
In addition:

- The target sample size is approximately 50 participants. An anticipated number of 60-80 patients will be screened to reach the target enrollment.
- Multiple sites will be used to recruit participants to be enrolled from the U.S.
- Source of participants will come from the primary investigators patient pools as well as the general public.
- Recruitment venues will include advertisement/flyer posting
- Advertisements will include local flyers

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.]

Data for patients lost to follow up/withdrawal will be collected if possible. Subjects in the ITT population but not in the mITT group will be represented in all tables except those for the primary and secondary endpoint analysis. Data from those withdrawing from or lost to follow-up in the mITT population will be used for the primary endpoint and, if there is at least one full day's worth of data on the number of SUI episodes available, then this subject will also be included in the analysis of change in number of SUI episodes. Attempts will be made to contact subjects withdrawing from or lost to follow-up to the mITT population to administer the QoL questionnaire. If successful these subjects will be included in the change in QoL analysis. For mITT subjects not completing the treatment phase, a "last observation carried forward" approach will be used (see section 10 "Statistical Considerations"). If it appears that there will not be 50 subjects in the PP population further recruitment and enrollment will be necessary.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or

termination, will be provided by the suspending or terminating party to <investigator, funding agency, the IND/IDE sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Since this study is a non-significant risk study, there are no stopping rules required.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements

Study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, IRB and FDA.

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

The study devices will be provided by the sponsor and delivered to the investigator. Device accountability and distribution records will be maintained. The product will be packaged to prevent contamination. The PI will be trained by Rinovum Subsidiary 2, LLC. personnel on device placement for the screening visit fit assessment. Participants will not be trained on how to use the device since the indications for use are OTC. They will be given the IFU and instructed to demonstrate insertion and removal under physician supervision to verify that they successfully completed the steps. The fit assessment will include participant input to demonstrate proper understanding of whether or not the device is appropriate for her.

The manufacturer of the device is Rinovum Subsidiary 2, LLC. Design Controls and Good Manufacturing Procedures shall be used in the manufacturing of the device, in accordance with 21 CFR part 820. The PI will give the participants 42 preweighed pads for the duration of the study. The PI will give participants 20 SUI devices. Participants will complete the baseline first wearing only preweighed pads and then complete the treatment phase, where participants will wear both a preweighed pad and an SUI device.

The SUI devices consist of the following:

- Device size(s): One size (Quantity: 20)
- Device model(s): SUI Pessary Device, Disposable, Single Use
- Preweighed pads will be provided to the participant (quantity: approximately 42)
- Duration of Use: The device will be used for a period of 12 hours
- Frequency of use: 14 consecutive days
- Double ziplock bags and shippers for mailing used pads to the study site for weighing

The storage and shelf life requirements for the Rinovum Subsidiary 2, LLC SUI Pessary device are as follows:

The device is made of plastic-like and silicone-like materials. These materials have a long history of use and have been shown not to deteriorate over time.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

A Device Accountability Form shall be used to document the following:

- Reconciliation of investigational device accountability;
- Verify that the device accountability documentation is accurate and complete;
- Arrange for return of all unused devices and clinical supplies to Rinovum Subsidiary 2, LLC. as applicable.

7 STUDY PROCEDURES AND SCHEDULE

This study will include the following procedures:

- Medical history
- Fit assessment to ensure that device is a proper fit and does not prevent voluntary voiding
- Physical examination (vital signs, height, weight, vaginal exam for vaginal infection evaluation)
- Vaginal swab to evaluate vaginal microflora
- Urinalysis to check for active urinary infection
- Urine Pregnancy Test (if applicable)
- Participants will be given an IFU and demonstrate insertion and removal of device under physician supervision
- Distribution of preweighed pads for the baseline phase
- Distribution of preweighed pads and devices for the treatment phase
- Return via mail all worn pads for weight recording
- Collection of study diaries, to be completed at home by the participant
- Quality of Life Questionnaire

7.2 LABORATORY PROCEDURES/EVALUATIONS

A urine pregnancy test, if applicable, will be performed no more than 24 hours prior to study intervention. A urinalysis will be performed to ensure no infections are active at the time of screening and at the end of treatment phase. Results of both urine pregnancy test and urinalysis test shall be made available prior to administration of study product.

A vaginal swab shall be obtained at the time of enrollment, before treatment phase, and after end of treatment phase to evaluate any changes in vaginal microflora.

7.3 STUDY SCHEDULE

Prior to enrollment, screening questions, a medical file review, a physical examination, pregnancy test (if applicable), urinalysis, and a human factors and a fit assessment will be used to determine/assess whether a participant meets the eligibility criteria. A vaginal swab shall be performed to establish baseline vaginal microflora. These activities must be performed within 1 week of enrollment. Informed consent will be obtained prior to any screening procedures. The human factors and fit assessment will include the following:

- Participant will perform self-insertion and removal in accordance with the IFU under supervision of physician
- Participant will provide feedback regarding the fit of the device based on the IFU description of proper fit without input of the physician
- Physician will verify device is a proper fit for participant after participant performs self-insertion (if physician determines the device is not a good fit for the participant, the participant may be terminated from the study)

Enrollment/Visit #1 schedule shall consist of the following:

- Provide participants with a description of what to expect with the study
- Participant will complete a Quality of Life Survey
- Provide the patient with a Baseline Study Diary for them to keep track of their leaking patterns for the first phase of the study
- Physician will administer 14 preweighed pads for the patient to wear for 7 consecutive days.
- Record any adverse events

NOTE: all worn pads will be placed in preweighed, double sealed, ziplock bags and returned to the clinical site via mail within 48 hours of use by the participant for weighing throughout the entirety of the study

NOTE: to minimize time between pad wearing and pad weighing, participants will be mailing back all worn pads immediately upon completion of the 7-day wear to the site. The site will record the pad weights in the Pad Weight Log form.

Visit #2 schedule shall consist of the following:

- Update Medical History, if applicable
- Perform a urine pregnancy test, if applicable
- Perform a vaginal swab for vaginal microflora assessment
- Assess for any symptoms of active vaginal infections requiring treatment (if a patient is symptomatic of a vaginal infection, they may be treated and enrolled at a later date once vaginal infection has resolved).
- Collect Baseline Study Diary from participant
- Go over a series of questions with participants
- Repeat the Quality of Life questionnaire
- Administer the Treatment Study Diary
- Physician will administer 20 devices and 28 preweighed pads to wear both device and pad simultaneously for 14 consecutive days.
- Record any adverse events

NOTE: to minimize time between pad wearing and pad weighing, participants will be mailing back all worn pads immediately upon completion of every 7-day wear to the site. The site will record the pad weights in the Pad Weigh Log form. If the participant returns for Visit #3 within 2 days of completing the 14-day wear, they may bring the remaining 7 worn pads to the visit in lieu of mailing in pads at the physician's discretion.

Visit #3 schedule shall consist of the following:

- Update Medical History, if applicable
- Perform a urinalysis and vaginal microflora swab
- Assess for any active vaginal infection
- Collect and review the Treatment Study Diary
- Collect and way any remaining worn pads, if applicable
- Complete the Final Questionnaire
- Complete the post-treatment Quality of Life Survey
- Record any adverse events

Procedures	Screening	Enrollment/ Baseline (Visit 1)[1]	Follow-Up (Visit 2)	Follow-Up (Visit 3)
Informed consent	X			
Demographics	X			
Medical history	X	X	X	X
Physical exam	X			X
Vital signs	X	X	X	X
Height	X			X
Weight	X			X
Human Factors and Fit Assessment	X			
Urine Pregnancy Test (if applicable)	X		X	
Urinalysis	X			X
Administer Investigational Product			X	
Adverse event evaluation		X	X	X
Vaginal swab	X		X	X
Questionnaire	X	X	X	X
Quality of Life Survey		X	X	X

(1) Enrollment must be take place within 1 week of screening. Otherwise, screening procedures must be repeated prior to enrollment

7.4 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

Prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications. This information shall be collected during the medical history collection. There are no known concomitant medications for the treatment of SUI. However, concomitant treatments include pelvic floor strengtheners, such as Apex, biofeedback treatments, and physical therapy for SUI.

7.5 JUSTIFICATION FOR SENSITIVE PROCEDURES

There are no drug or food interactions for this study. Participants should not use the device while using a tampon, diaphragm, or other vaginal device.

7.6 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable.

7.7 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable.

7.8 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Participants will not have continued access to the study agent at study closure.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

An adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether considered intervention-related (21 CFR 312.32 (a)).]

A Serious adverse event (SAE) is defined as an AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An unanticipated adverse device effect (UADE) is defined 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 participants (21 CFR 812.3(s)).

8.2 CLASSIFICATION OF AN ADVERSE EVENT

All AEs will be assessed by the PI using a protocol defined grading system. Describe the method of grading an AE for severity. For example, many toxicity tables are available for use and are adaptable to various study designs.

The following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

The PI's assessment of an AE's relationship to study device is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- **Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 REPORTING PROCEDURES

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the DCC/study sponsor

within 24 hours of site awareness. See **Section 1, Key Roles** for contact information.
- Other SAEs regardless of relationship, will be submitted to the study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.
The study sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

8.5 STUDY HALTING RULES

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.
Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.
The study does not contain specific halting rules; however, the PI and monitor may halt the study due to AE/SAE analysis.

8.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a clinical monitor with the appropriate expertise, including. The monitor and the sponsor will assess efficacy and safety data.

9 CLINICAL MONITORING

Clinical site monitoring shall be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s). Monitoring for this study will be performed by a sponsor representative. Details of clinical site monitoring are documented in a CMP. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring

reports. Monitoring Plans may vary slightly for each study site due to each study agreement. Independent audits will be conducted to ensure clinical practices are performed consistently across all participating sites.

10 STATISTICAL CONSIDERATIONS

10.1 Populations

Intent to Treat Population (ITT): Any subject enrolled who gets a pre-weighed pad for the control phase. This is expected to be 60-70 subjects.

Modified Intent to Treat Population (mITT): Any subject enrolled who gets through the control phase, is given the device and pads for the treatment period, and who uses the device such that there is at least one data point to analyze - i.e., use of the pad for at least one hour during the last 7 days of the treatment period. A subject who is not in the study at the beginning of the last 7 days of the treatment period is in the ITT population but not the mITT population. The mITT IS THE POPULATION THE ANALYSIS WILL BE DONE ON.

Per Protocol Population (PP): Any subject getting through the entire treatment period and has complete data (i.e., pad weight reduction data for the last 7 days of the treatment period). For example, someone having only data for 6 out of the last 7 days of the treatment period is in the mITT population but not the PP population.

Safety Population (SP): Same as ITT.

10.2 Data Description and Presentation

A statistical analysis plan (SAP) will be developed specifying in more detail the analyses for the study. It will be comprised of a text section and a tables/listings/figures section. The text will prescribe the outputs reported in the tables and figures; the listings will report all the data on the case report forms and other external data (Excel reports of laboratory data, diaries, etc.). All programming will be done in SAS Version 9.4.

All results will be summarized descriptively. Continuous variable results will be tabulated using means, medians, standard deviations, minimums and maximums. Categorical variables will be summarized using the number of observations and percentages. p-values will be reported, where appropriate, to four decimal places.

Intermediate calculations will not be rounded. Internal computer precision will be kept and the final values will then be output, formatted to the relevant whole number and decimal precision.

10.3 Sample Size and Study Outcome Determination

A precision approach will be used to determine the appropriate sample size and power for the study. For power and sample size considerations a type 1 error rate (alpha) of 0.05, one-sided, will be used. Given a sample size of 50 the calculations have been done with various standard deviations to show power below and above 90% (see Table 1 below). Sixty to seventy participants will be enrolled to allow for the fifty per-protocol participants, although the analyses will be done on the mITT population.

The assumptions made for the power and sample size computations come from the Poise study (Ziv et al), where their assumption for the effect size was reduction in pad weight gain per 8 hours of 70%, with a standard deviation of 15%. The results of the study showed an 86% reduction in pad weight gain per 8 hours with a 9% standard deviation. Given those results, this study's assumptions of 60% improvement and a range of standard deviations from 15% to 20% appear conservative; thus, the expected results would indicate a successful outcome for the primary endpoint.

The computations below are based on the precision method, which in the case of this study computes a lower 95% confidence limit for the percentage change. Here we consider a changes around 60% in the explanation of the table. Different standard deviations are used with the sample size of 50.

Table 1.

n	½ width of CI	Std Dev	Power
50	5	16	0.999
50	5	17	0.991
50	5	18	0.956
50	5	19	0.869
50	5	20	0.720
50	6	20	0.995

The first entry in the table shows that if the resulting mean reduction in pad weight gain was 60% and the standard deviation of the mean percentage change was 16%, the lower limit of the 95% confidence interval for 60% would be 55%: 60% - 5% (½ width), with 99.9% probability (power). The last line in the table above shows that the resulting mean percentage change would have to be greater than 56 for the power to be 99.5% (56% - 6% ½ width = 50%, not greater than 50%) if the standard deviation was 20%. If the result was 60% the lower limit of the confidence interval would be 54%: (60% - 6%) with 99.5% power. Thus, for all lines above except 4 and 5 the endpoint was reached with greater than 90% power.

A successful outcome for this endpoint would be any result where the lower limit of the 95% confidence interval is above 50% with more than 90% power, as explained above. When the results are tabulated, another table will be created with the n's and standard deviations from the study for comparison to the study results.

Also, this sample size should also be sufficient for inferential analysis of the secondary endpoints.

10.4 Statistical Hypotheses and Data Description

1. Type 1 Error and Multiplicity Concerns:

The inferential tests for the one primary and two secondary endpoints were initially conceived to be one-sided using alpha=0.05. Since the sponsor wishes to use the success of all three for labeling and marketing purposes, a Bonferroni adjustment for multiple comparisons will be employed. Thus, statistical significance will be indicated for each endpoint if the p-value is less than 0.0167.

2. Primary Endpoint:

There is one primary endpoint, for efficacy. The objective is to show that reduction in the mean pad weight gain per hour is >50% in the treatment period. Thus, the null hypothesis is that the mean weight gain reduction per hour is <=50%, and the alternative is that it is >50%, from the control period (no device) to the treatment period (women wearing the device). The data values will be computed for each woman as:

[(total weight of all pads worn during the treatment period/hrs. pads are worn during treatment)

minus

(total weight of all pads worn during the control period/ hrs. pads are worn during control)]

The above quantity divided by
(total weight of all pads worn during the control period/ hrs. pads are worn during control)

This resulting quantity is then multiplied by 100.

Ex. Subject's total pad weight for control period is 140 grams. Pads were worn for a total of 100 hours. Weight/hr. is 140/100 = 1.4 g/hr. Subject's total pad weight for treatment period is 60 grams. Subject wore pads for 100 hours. Pad weight per hour is 60/100 is 0.6 g/hr. Difference, treatment – control is 0.6 -1.4 = -0.8 g/hr. For the percent change, 100*(-0.8/1.4) = -57.143%. Therefore the reduction in pad weight gain is 57.143%.

The null hypothesis will be that the mean reduction in pad weight gain per hour is less than or equal to 50%, with the alternative that it is greater than 50%. If the raw percentage change data appear to be normally distributed, a paired t-test will be used to test the hypothesis. If not, see section 10.6 (2).

The precision method will be utilized to determine success. The precision approach creates a lower bound for a confidence interval that is higher than the reference, in this case 50%. This 50% standard was chosen based on the FDA guidance document.

Power and sample size calculations determine scenarios of success. When the resulting mean reduction in pad weight gain per hour is quantified, its lower limit of a (1-0.0167)% confidence level is determined. This value is then compared to parameters determined to be efficacious in the sample size calculations (section 10.3). It is expected that the mean reduction per hour will be >50% such that the lower limit of the confidence interval for that result will be higher than 50% with adequate power to suggest success for the study.

3. Secondary Endpoints:

   a. For the change in SUI episodes endpoint each subject will have a change in the number of episodes per day from the control period to the treatment period. Specifically, the number of episodes will be recorded each day in the diary. For the control phase, there will be (at most) 7 days of data. The mean number of SUI episodes per day will be computed for each subject. The same measures

will occur in the treatment period for the analysis period, the last 7 days. Each subject will again have a mean number of SUI episodes per day. If the pads are not worn for the entire time specified during a day, the fraction of the day the pads are worn will be used in computing the number of days. Therefore, there will be, say, 50 differences comprised of mean number of SUI episodes per day in the treatment period minus mean number of SUI episodes per day for control period. (These numbers will likely be negative.) The mean of these 50 mean differences represents the mean change in the number of SUI episodes per day from the control period to the treatment period. The null hypothesis will then be that the mean change in the number of SUI episodes is 0, and the alternative is that it is less than 0, analyzed using a paired t-test. A p-value of less than 0.0167 indicates success.

b. For the quality of life score there will be three measures as described in the visit schedule above. For descriptive purposes the results and change from the previous visit will be shown, as well as the change from the enrollment visit to the post-treatment visit. The changes will likely be negative scores as the QOL is expected to improve, as the instrument records lower numbers as indicating a better quality of life. For the purposes of inferential analysis, a mixed model analysis of variance on the scores will be used on the result at time t (t=baseline, post-control, post-treatment) with time as a fixed effect and subject as a random effect. Thus, the null hypothesis is that there is no significant difference from baseline/enrollment to post-treatment, i.e., that the mean change in score is 0. The alternative is that this change is less than 0. Correlation of scores within subjects will be considered as compound symmetric. The p-value indicating the significance of the least square mean score at the third time-point compared to that at the first time-point will determine if the endpoint is met.

All inferential testing will be done on the mITT population and will be one-sided. As noted above statistical significance will be reached if the relevant p-value is less than 0.0167. Results for all populations will be reported.

There is a secondary safety endpoint as described earlier in the protocol. Safety reporting using urinalysis, vaginal swab, vaginal examination, and evaluation will be descriptive and narrative in nature.

Similarly, exploratory endpoint results of comfort and successful use will be descriptive. No inferential hypotheses will be used here.

10.5 Analysis Data Sets

Data will be combined into analysis data sets in a form similar to the CDISC ADaM structure, from which all outputs will be generated. It is anticipated there will be the regular subject level data set (similar to ADSL), an efficacy data set (similar to ADEF), a laboratory data set (similar to ADLB), an adverse events data set (similar to ADAE), and perhaps others.

10.6 Description of Statistical Methods

1. Adjustment for non-normality:

    a. The primary endpoint analysis is based on the mean pad weight reduction per hour as a percent having a normal distribution. Values will be checked for normality via the Kolmorgorov Smirnov test, and a transformation may be needed prior to the analysis. First the percent change from baseline will be examined, and if the data are not normally distributed then a log transform of the ratio of the post-treatment result to the post-control will be utilized. The standard error of this logged quantity and resulting lower bound of the 1- (adjusted alpha) confidence interval will be determined. Then this lower bound will be exponentiated to get the ratio in the original data units. 100 times this value can now be interpreted as the percent of the post-treatment result that is left from the baseline. This is because the post-treatment result will be less than the post-control result. Subtracting this result from 100% will give the lowest percentage value needed to achieve statistical significance. If this lower bound is greater than 50% and the raw percent change from baseline is greater than this result then the primary endpoint has been reached.

        The expected results suggest that the percent change from baseline should be normal, thus validating the sample size and power calculations. Since those assumptions are conservative it is felt that any transformation of the data and subsequent modification of the analysis (e.g., see adjustment for site below) still allow for this endpoint to have sufficient power.

    b. Secondary Endpoints:

        i. Should the difference in SUI episodes be non-normal then the natural log of the baseline and treatment phase scores will be taken and the natural log of the ratio of the post-treatment result to that of the baseline will be analyzed in the same fashion as described in “a” above. A raw difference of 0 would translate to a ratio of 1.0 after exponentiation back. Since the difference is expected to be negative, the upper bound of the raw (transformed back) is compared to 1. If it is less than the endpoint has been reached, indicating that the treatment mean is statistically significantly less than the control mean.
        ii. If the scores of the QOL indicate a significant difference from normality then a natural log transformation will be done and modeled

2. For the other secondary analysis (safety outcomes examination) descriptive and possibly narrative results will be presented. For the exploratory outcomes of comfort and successful usage results will be reported similarly. Details will appear in the SAP.

Results for the primary and secondary endpoints will be presented in tables, with continuous data exhibited via descriptive summaries (n, mean (std), median, min, max); n will be a whole number, means, medians, and minimum and maximum values will have one decimal place, and standard deviation will have two. Categorical measures (counts) reported as n (%), with n being a whole number and the percent having one decimal place.

As mentioned above, the analyses for the primary and two secondary endpoints will be done on the mITT population and no imputation should be necessary. For the primary endpoint and the SUI episodes secondary endpoint, by definition, the subject must have participated on one day of the treatment period; therefore, there will be a pad weight gain per hour measure and (conceivably) a diary entry for the number of SUI episodes; both of these would be the values for analysis for that subject. If they are not retrievable then they are missing. If a withdrawing mITT subject is able to complete the quality of life questionnaire that data would be used; if not that subject has a missing value for the post-treatment QOL score. Should participants withdraw replacements will be utilized until 50 per protocol participants have completed the study. Possible screening for as many as 80 participants should provide this needed sample size. No covariate use is planned for any analysis.

10.7 Adjustment for Site

The study may be performed at more than one site. If so the effect of site will be investigated in each of the analyses above.

For the principal endpoint analysis, a fixed effects model with site as the effect will determine if the percentage change from baseline or log of the ratio of post-treatment result to baseline result as the outcome will need to be adjusted for that effect. A p-value of <= 0.05 will constitute statistical significance of the site effect.

The same analysis will be done for the mean change in SUI episodes per day secondary endpoint analysis. Site will be a fixed effect modeling each subject's change in mean number of SUI episodes per day.

For the quality of life repeated measures ANOVA site will again be included in the model as a fixed effect.

Should site become statistically significant in any of the analyses then it will be used as a fixed effect factor in all three analyses, and the appropriate percentage and mean changes (or log transformations implementing those analyses) will be extracted from the output created by the models.

10.8 Adverse Events

No formal testing of adverse events or their characteristics will be performed. Reporting is described above. The latest version of MedDRA will be used for coding. The section of tables will include a summary table, a system organ class/preferred term table, and tables for relationship and severity to study treatments.

10.9 Interim Analyses and Stopping Criteria.

No interim analyses are planned, and the study will be run to its completion unless stopped for safety considerations.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. As part of participating in a NIH IC-sponsored or NIH IC -affiliated study, each site will permit authorized representatives of the NIH IC and regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity. Describe in this section who will have access to records.

12 QUALITY ASSURANCE AND QUALITY CONTROL

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Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant, and written documentation of informed consent is required prior to starting intervention/administering study product. The following consent materials are submitted with this protocol Rinovum Subsidiary 2, LLC. SUI Device Efficacy and Safety Study Informed Consent.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have

the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the East Suburban OB/GYN Facility. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the [insert institution] research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the [insert institution].

13.5 FUTURE USE OF STORED SPECIMENS

Data collected for this study will be analyzed and stored at the [insert institution] facility. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Sponsor's facility under the supervision of the Director of Regulatory and Quality for use by other researchers including those outside of the study. Permission to transmit data to the will be included in the informed consent.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the CRF will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the CRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Case Report Forms manually.

14.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.
These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 3 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported the Sponsor. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.]

14.4 PUBLICATION AND DATA SHARING POLICY

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human participants to intervention or concurrent comparison or control groups to study the cause-and-effect

relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric post-market surveillance studies.

NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.]

15 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.

16 LITERATURE REFERENCES

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