RECKITT

CLINICAL INVESTIGATION TITLE

A two-arm, parallel-design, clinical investigation to determine the effectiveness and safety of a water-based personal lubricant with a sensory action and silicone-based personal lubricant with a sensory action for the relief of intimate discomfort associated with vaginal dryness.

Short Investigation Title

Effectiveness and safety of a water-based and a silicone-based personal lubricants with sensory action.

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INVESTIGATOR STATEMENT

I have read and understood this Clinical Investigation Plan (CIP) and agree:

- to conduct this clinical investigation in accordance with the CIP and to abide by all provisions of this CIP (including other manuals and documents referenced from this CIP). Amendments to the CIP are acceptable only upon mutual agreement with the exception of urgent safety measures that need to be taken to protect investigation subjects from any immediate hazard to their health and safety.
- to conduct this clinical investigation in accordance with the principles as set out in the Declaration of Helsinki and with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), ISO 14155:2020 and applicable regulatory requirements.
- to conduct this investigation only after a favourable opinion is obtained from the Ethics Committee and Regulatory Authority.
- to conduct this investigation in accordance with General Data Protection Regulation (GDPR) requirements.
- to report all information or data in accordance with the CIP.
- to report any serious adverse events and device deficiencies that may have led to a SAE as defined in the "Safety Reporting" section of this CIP.
- to handle all medical device supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the CIP.

I understand:

- that information that identifies me will be used and disclosed as described in the CIP and that such information may be transferred to countries that do not have laws protecting such information.
- that since the information in the CIP and the references in the Investigator's brochure (if applicable) are confidential, its disclosure to any third parties, other than those involved in approval, supervision or conduct of the investigation is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

Principal Investigator

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LIST OF ABBREVIATIONS

Abbreviation	Abbreviation in Full
ADE	Adverse Device Effect
AE	Adverse Event
AEMT	Adverse Event Management Team
ASCO	American Society of Clinical Oncology
BMI	Body Mass Index
BSRA	Biological Safety Risk Assessment
CCO	Cancer Care Ontario
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CFR	Code of Federal Regulations
(e)CRF	Electronic Case Report Form
CRO	Clinical Research Organisation
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSFI	Female Sexual Function Index
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HRT	Hormone Replacement Therapy
HPV	Human Papillomavirus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMSU	Investigational Materials Supplies Unit
IP	Investigational Product
IRB	Institutional Review Board
ISO	International Organisation for Standardisation
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
MCID	Minimum Clinically Important Difference
MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
MII	Mean Irritation Index
NRS	Numeric Rating Scale
PGIC	Patient Global Impression of Change
PMS	Post Marketing Surveillance
PP	Per Protocol
PT	Preferred Term

Abbreviation	Abbreviation in Full
QoL	Quality of Life
RA	Regulatory Authority
R&D	Research and Development
REC	Research Ethics Committee
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPQ	Subject Perceived Questionnaire
STI	Sexually Transmitted Infection
TEADE	Treatment-Emergent Adverse Device Effect
TEAE	Treatment-Emergent Adverse Event
USADE	Unanticipated Serious Adverse Device Effect
VET	Vaginal Epithelial Tolerability
VAS	Visual Analogue Scale
VRS	Verbal Rating Scale
VVA	Vaginal/Vulva Atrophy
WHO	World Health Organisation

CLINICAL INVESTIGATION SYNOPSIS

Investigation Title:	A two-arm, parallel-design, clinical investigation to determine the effectiveness and safety of a water-based personal lubricant with a sensory action and silicone-based personal lubricant with a sensory action for the relief of intimate discomfort associated with vaginal dryness.
Reckitt Investigation Number:	5025003
Background and Rationale:	[redacted] To comply with the MDR, two personal lubricants, [redacted], will be investigated.

Objectives:	The primary objective of this investigation is to demonstrate the effectiveness of two personal lubricants when used as intended during vaginal intercourse in women who experience intimate discomfort associated with vaginal dryness. The secondary objectives of this investigation, are as follows: • To assess subject's perception of two personal lubricants when used during vaginal intercourse in women who experience intimate discomfort associated with vaginal dryness. • To assess subject's global evaluation of two personal lubricants when used during vaginal intercourse in women who experience intimate discomfort associated with vaginal dryness. • To assess male partners' perception of two personal lubricants when used during vaginal intercourse. • To assess the effects of two personal lubricants on the impression of change in the sexual intimacy between female subjects and their male partners. • To assess vulvovaginal tolerance of two personal lubricants in women who experience intimate discomfort associated with vaginal dryness. • To assess oral mucosal tolerance of two personal lubricants in women who experience intimate discomfort associated with vaginal dryness. • To assess the safety and establish the safety profile of two personal lubricants in women who experience intimate discomfort associated with vaginal dryness. • To assess the safety and establish the safety profile of two personal lubricants in males. [redacted]

Primary Endpoint:	The primary endpoint of this investigation is the change from baseline in total Female Sexual Function Index (FSFI) score at 4 weeks. An increase of at least 4 (≥4) points in the FSFI score from baseline to 4-weeks post-lubricant use is considered a clinically important change.

Secondary Endpoints:	The secondary endpoints of this clinical investigation, are as follows: • Number and percentage of subjects who achieve at least 4-point (≥4) increase in total FSFI between baseline and 4 weeks. • Number and percentage of subjects who transition from sexual dysfunction (≤26.55 total FSFI score) to sexual function (>26.55 total FSFI score) between baseline and 4 weeks. • Change from baseline in individual domain scores (Pain, Lubrication, Desire, Arousal, Satisfaction, Orgasm) at 4 weeks. • The subjects' perception of two personal lubricants determined through Subject Perceived Questionnaire (SPQ) after first product use (within 24 hours of intercourse) and at 4 weeks. • Subject Global Evaluation of product effectiveness, tolerability, and device usability (included in the SPQ) at 4 weeks. • The male partners' perception of two personal lubricants determined through Subject Perceived Questionnaire (SPQ) after first product use (within 24 hours of intercourse) and at 4 weeks. • Number and percentage of female subjects recording ≥2 improvement in sexual intimacy on the Patient Global Impression of Chang (PGIC) at 4 weeks. • Number and percentage of male partners recording ≥2 improvement in sexual intimacy on the PGIC at 4 weeks. • An assessment of the Vaginal Epithelial Tolerability (VET) of the two personal lubricants at baseline, 2 and 24 hours post single application as assessed by gynaecologist examination. • Subject Perception of Vulvovaginal Tolerance of the two personal lubricants will be determined through Subject Perceived Questions at 24 hours post single application. • Global Assessment of Vulvovaginal Tolerance for each subject at 24 hours post single application as determined by the gynaecologist. • Overall Vulvovaginal Tolerance Rating Statement for each personal lubricant as determined by the gynaecologist. • An assessment of the Oral Mucosal Tolerance of the personal lubricants at baseline, 30 minutes, 2 and 24 hours post single application to the upper and lower inner lip as assessed by dermatologist.

	• Subject Perception of Oral Mucosal Tolerance of the two personal lubricants will be determined through Subject Perceived Questions at 24 hours post single application. • Global Assessment of Oral Mucosal Tolerance for each subject at 24 hours post single application as determined by the dermatologist. • Overall Oral Mucosal Tolerance Rating Statement for each personal lubricant as determined by the dermatologist. • Overall proportion of subjects with Adverse Events/Adverse Device Effects (AEs/ADEs) i.e. the occurrence of one of more AE/ADE per subject. • Overall proportion of males with Adverse Events/Adverse Device Effects (AE/ADEs) i.e. the occurrence of one of more AE/ADE per male partner. [redacted]
Success Criteria:	Observation of a statistically significant and clinically important change from baseline in total FSFI score at 4 weeks. A pre-specified minimum clinically important difference (MCID) is at least 4 (≥4) points from baseline to 4 weeks.
Design:	This is a two-arm, parallel-design clinical investigation determining the effectiveness and safety of two personal lubricants. This clinical investigation consists of two phases, a Tolerance Phase and a Treatment Phase, whereby a subset of subjects and their male partners will enter both the Tolerance Phase followed by the Treatment Phase. The remaining subjects and their partners will enter the Treatment Phase only.

Subjects:	In this synopsis, female participant is referred to as the subject. Information on the activities undertaken by the male partner is specifically noted. The investigation population will include an approximate 1:1 ratio of pre-menopausal to post-menopausal, with a difference of up to 40:60 (up to a maximum of 60% in either sub-population) being allowed. 33 subjects will be randomised to each treatment group. A subset of 22 subjects will be selected in a 1:1 treatment allocation ratio to participate in the Tolerance Phase of the investigation. **Summary of Inclusion and Exclusion Criteria:** Only subjects to whom all the following conditions apply will be included: <u>Universal Inclusion Criteria:</u> 1. Subject and their male partner have provided written informed consent. 2. Subject is female and both subject and their male partner are aged at least 18 years. Maximum age of female subject is 65 years. 3. Female subject and their male partner in a mutually monogamous heterosexual relationship (≥ 3 months) who are sexually active, defined as having sexual intercourse at least once a week. (Note: The number of sexual intercourses may comprise twice in one week to account for a menstrual period break.) 4. Female subject that agrees to have a gynaecological pelvic examination to ensure no significant disease findings and have intact skin and mucous in the test region (vaginal and vulvar / intimate area) except skin dryness as visually assessed by the gynaecologist at all the relevant time points. 5. Female subject that agrees to an oral exam by a dermatologist to ensure no significant disease findings and have intact skin and mucous in the test region (oral cavity - including lips, inside lining of the lips, cheeks (buccal mucosa), teeth, gums, tongue, the floor of the mouth, roof of the mouth (hard palate) and area behind wisdom teeth (retromolar trigone). 6. Subjects reporting mild to moderate vaginal dryness and dyspareunia during sex (when not using lubricant) in the past 3 months as confirmed by a score of 1 or 2 for vaginal dryness and 1 or 2 for dyspareunia on the Verbal Rating Scale (VRS) of dyspareunia and vaginal dryness.

	Pre-menopausal Inclusion Criteria: 1. Female subject of childbearing potential who is willing to use a highly effective method of contraception throughout the clinical investigation. A female is considered to be of childbearing potential following menarche and until becoming post-menopausal unless permanently sterile by methods including hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A highly effective method of contraception is defined as a method that can achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods include combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal and transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable and implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner (who has received medical assessment of the surgical success). Post-menopausal Inclusion Criteria: 1. Female subject in post-menopausal phase defined as having amenorrhea (absence of menstruation) for at least 12 consecutive months without an alternative medical cause. 2. Female subject with premature menopause – due to surgical menopause or physiological menopause within the last 12 consecutive months of the screening visit (diagnosis to be confirmed as irreversible in subjects' medical history) or after having received chemotherapy. Subjects to whom any of the following conditions apply must be excluded: Universal Exclusion Criteria: 1. Female subject or their partner who has previously experienced an irritant or allergic reaction to any personal lubricant, vaginal moisturiser or female hygiene product or known to have any contact allergy or allergy/ hypersensitivity to the test product ingredients. 2. Female subject with history of mucosal intolerance to warming agents.

	3. Female subject with continuous or intermittent oral allergy syndrome or burning mouth syndrome, or history of thereof (self-reported). 4. Female subject with urinary, vaginal infection (fungal, bacterial) or sexually transmitted infection at screening visit, which in the opinion of the investigator would affect the study outcomes or the safety of the subject. 5. Female subject that has any condition of the oral cavity, including oral infection, active oral herpes simplex virus, active canker sores or oral ulcers and erosions as determined by the investigator. 6. Female subject who has had a positive cervical screening examination for human papillomavirus (HPV) within the 3 years of the screening visit (medical history/self-reported). 7. Female subject presenting with signs of internal irritation, active psoriasis, lichen sclerosis, eczema or other active skin disorder upon clinical examination. 8. Male partner of female subjects has broken skin or wounds in the intimate area (self-reported). 9. Female subject with a history of skin disorder, which in the opinion of the investigator will affect study outcome. 10. Female subject presenting clinically abnormal findings other than irritation e.g. lumps, open sores or blister type wounds during the physical examination (including the gynaecological examination) that in the opinion of the investigator will affect study outcome. 11. Female subject that has had a suspicion of malignancy or history of malignancy within the past 2 years (self-reported). 12. Female subject with autoimmune conditions or any medical conditions which in the opinion of the investigator could compromise the immune function. 13. Female subject who has had surgical cervical excision or vaginal and/or vulvar procedures, including laser and cosmetic procedures to the vulva or vagina in the previous year. 14. Female subject that has any tooth ache or other dental/oral malady (self- reported). 15. Female subject with ongoing dental/orthodontic procedures or any medical/surgical interventions involving the oral cavity (self-reported).

	16. Female subject currently being treated with systemic medications or medicines (e.g. glucocorticosteroids, antibiotics, local oestrogen and other intravaginal products) that are acting locally in the vaginal area which may influence the clinical study outcomes. 17. Female subject who has started, stopped, or changed hormonal treatments (for contraception, vaginal dryness, or any other condition) during the previous 3 months prior to screening or those intending or expecting a change in treatment during the investigation. 18. Female subject who has used any kind of topical histamine and/or topical hormonal based product in the form of an intravaginal cream or moisturiser for local treatment of vaginal dryness in the past 3 months. 19. Female subject taking steroid preparations, immunosuppressants or any other medication which in the opinion of the investigator may affect the test results: a. Anti-inflammatory or antihistamine within 1 week prior to the screening visit. b. Cough suppressants or corticosteroids within 4 weeks prior to screening visit. c. Retinoids or immune suppressants within 6 months prior to screening visits. 20. Female subject who has had any change to medication or treatment regimen for the treatment of diabetes mellitus during the previous 3 months prior to screening. 21. Female subject using non-medicated, over the counter product, herbal/natural remedies on the vulva, vaginal opening and inside the vagina and is unwilling to stop at least 7 days prior to screening and throughout the duration of clinical investigation. 22. Female subject showing vaginal prolapse and/or other medical conditions that could interfere with the investigation conduct and participation. 23. Female subject using vaginal douches and is unwilling to stop its use at least 2 weeks prior to screening and throughout the duration of the clinical investigation. 24. Female subject or their male partner that, in the opinion of the investigator, will be unable to comply fully with the study

	requirements or unable to tolerate the procedures described in the CIP. 25. Female subject has participated in another investigation where a medicinal, medical device clinical investigation or any form of studies involved testing on female intimate area within 3 months prior to screening. 26. Female subject or their male partner has received an investigational product or participated in another trial involving a marketed or investigational drug in the 30 days (or for investigational agents with a long half-life, a washout of 5 half-lives) prior to screening. Or if the investigator believes that any previous participation in an investigational study would be to the detriment of the safety of the participant or the conduct of the study. 27. Female subject or their male partner who is an employee at the site or a partner or first-degree relative of the Investigator. 28. Female subject or their male partner fails to satisfy the investigator of fitness to participate for any other reason. <u>Pre-menopausal Exclusion Criteria:</u> 1. Female subject who is pregnant (as confirmed by a positive pregnancy test), breast-feeding or trying to conceive. <u>Post-Menopausal Exclusion Criteria:</u> 1. Female subject that has had previous episodes of vaginal bleeding of unknown origin within the last 6 months of the screening visit. <u>Tolerance Subset - Exclusion criteria for Enrolling into Treatment Phase</u> Subjects participating in the Tolerance Phase who have any of the following conditions must not continue to the Treatment Phase. 1. Any observed severe irritancy reactions at any time point. 2. Any reaction failing to adequately resolve or needing further treatment, that in the opinion of the investigator represents an unacceptable risk to proceed with the investigation. 3. Any adverse events considered related to the investigational product that are serious and/or severe in nature that in the opinion of the investigator represent an unacceptable risk to proceed with the investigation.

Product(s) to be Evaluated and Treatment Regimen:	The following investigational products (IP) will be evaluated in this investigation: • IP A: [redacted] • IP B: [redacted] The following comparator will be used in the Tolerance Phase: • Comparator A: non-sensate water-based lubricant • Comparator B: non-sensate silicone-based lubricant According to the randomisation schedule, each subject will test one IP and the respective comparator in the Tolerance Phase and will test one IP in the Treatment Phase. <u>Tolerance Phase</u> Subjects assigned to complete the Tolerance Phase are expected to apply a single application to assess tolerability: • Approximately 3 g amount of IP to the vagina and intimate area for vulvovaginal tolerance. • A pea-sized application of IPs and comparators to the inner linings of the upper and lower lips of the subject's mouth for oral mucosal tolerance. <u>Treatment Phase</u> Approximately 3 g amount of IP will be considered as single application. Subjects will be expected to apply the IP when engaging in sexual intercourse, at least once a week over a 4-week period. This is to be able to assess key dimensions of sexual function of subjects.

Methodology:	**Visit 1 – Screening Visit:** All subjects and male partners will attend a screening visit to assess eligibility. Eligible subjects and their male partners will either enter the Tolerance Phase or directly into the Treatment Phase. **<u>Tolerance Phase</u>** The Tolerance Phase consists of a 7-day wash-out period followed by two further visits. **7-day wash-out period:** Subjects will not be permitted to use any personal lubricants or other remedies for vaginal dryness and will be asked to refrain from engaging in vaginal sex or any other vaginal penetrative sexual activity e.g. digital stimulation or use of sex toys. Subjects will also be prohibited from using any new oral products that are irregular to their normal dental hygiene routine or eating any new foods outside their normal diet. **Visit 2:** At the clinical site, subjects will be provided with a snack and drink, ahead of an oral water rinse. After the oral water rinse the subjects will participate in an additional 30-minute oral wash-out period which they will be asked to refrain from using any oral products or consuming any foods/drinks. If necessary, subjects may have water, and this will be recorded. Oral examination will be carried out by the dermatologist at baseline, 30 minutes, and 2 hours after a single application of the allocated IP and the respective comparator. Gynaecological assessments, including VET, [redacted] will be carried out by the gynaecologist at baseline, 2 hours post application of the allocated IP. After which subjects can leave the clinical site. **Visit 3:** 24 hours post application, subjects will return to the clinical site. The continued eligibility will be reconfirmed and above clinical assessments (oral examination, VET, [redacted] and the completion of a SPQ - Tolerance Phase will be performed. The gynaecologist will complete a Global Assessment of Vulvovaginal Tolerance for each subject and provide an Overall Tolerance Rating Statement for each IP upon completion of the Tolerance Phase. The dermatologist will complete a Global Assessment of Oral Mucosal Tolerance for each subject and provide an Overall Tolerance Rating Statement for each IP and comparator upon completion of the Tolerance Phase. After which subjects will move into the Treatment Phase of the investigation. **<u>Treatment Phase</u>**

	The Treatment Phase consists of a 4-week run-in phase, followed by two further visits. **Run-In Phase:** During this run-in phase, subjects will be asked to refrain from using any personal lubricants or remedies for vaginal dryness during sexual activity. Subjects will be asked to consent to engaging in vaginal penetrative sex at least once per week during this 4-week period. Subjects will be asked to record into their diary the number and frequency of coital acts during this period, including when subjects were unable to have sexual intercourse without the use of a lubricant and/or for menstrual bleeding (pre-menopausal women). **Visit 2*:** Subjects will return to the clinical site, where continued eligibility will be reconfirmed. After which subjects will be asked to complete the FSFI as baseline assessment. [redacted] Subjects will then be provided with their allocated IP to use at least once a week for vaginal penetrative sexual intercourse over a 4-week period. Subjects will also be issued a diary to record the investigation compliance e.g. number and frequency of vaginal penetrative sex occasions, IP use etc. The SPQ – Treatment Phase will be provided to subjects. An SPQ – Treatment Phase should be completed by the subject and the male partner after first use of the product within 24 hours of penetrative intercourse. **Visit 3**:** Subjects and male partners will return to the clinical site, where continued eligibility will be reconfirmed. For subjects, the following clinical assessments will be performed: Gynaecological/Pelvic examination (if necessary, in the opinion of the Investigator), [redacted] completion of FSFI, completion of SPQ – Treatment Phase, completion of Global Evaluation of Product Effectiveness, Tolerability and Usability and completion of PGIC. For male partners, they will complete the SPQ – Treatment Phase and PGIC. There after couple's involvement in the investigation will be complete. Adverse events and concomitant medication will be recorded throughout the investigation. * Visit 4 for subjects undergone the Tolerance Phase ** Visit 5 for subjects undergone the Tolerance Phase

Statistical Evaluation:	For the primary endpoint, within each of the treatment groups, the total FSFI score at 4 weeks will be compared to baseline using a paired t-test. Two separate null hypotheses that there is no difference compared to baseline (one per treatment group) will be tested. For the determination of the statistical significance of each comparison, an adjustment for multiple testing will be made according to the Bonferroni-Holm method to ensure the Family Wise Error is controlled at 5%. The mean change from baseline in total FSFI will be presented with Bonferroni-corrected 97.5% confidence intervals to account for the 2 treatment comparisons. If the within-subject differences are not normally distributed, a Wilcoxon signed rank test will be used to compare change from baseline. In this case, Hodges-Lehmann 97.5% confidence intervals will be calculated. The number and percentage of subjects (including a 95% confidence interval) achieving at least 4-point improvement in total FSFI at 4 weeks will be presented by treatment group and overall. This will indicate the percentage of subjects who achieved the pre-defined MCID. Similarly, the number and percentage of subjects who move from the sexual dysfunction (total FSFI ≤26.55) to sexual function (total FSFI >26.55) classification between baseline and 4 weeks will be presented by treatment group and overall. The secondary endpoints of the individual FSFI domain scores at 4 weeks will be compared to baseline using either a paired t-test or Wilcoxon signed rank test. AEs/ADEs from both the Tolerance Phase and Treatment Phase will be summarised together. Summaries will include incidence, severity and relationship to device and study procedures of treatment emergent adverse events and adverse device effects.

1 BACKGROUND AND RATIONALE

1.1 Background for the Investigation and Rationale

Healthy female genital tissue structure, function and integrity is maintained through the actions of a series of hormones collectively known as oestrogens; with their actions being mediated through oestrogen receptors present in the epithelial, endothelial and smooth muscle cells of the genital tissues. Oestrogens maintain the thickness of vaginal epithelium while promoting collagen and elastin synthesis i.e. structural supports, in vaginal connective tissue (collagen ensures tissue elasticity, pliability, thickness and tone of the vaginal area). Furthermore, in a healthy and well oestrogenised vaginal environment, the normal vaginal flora hydrolyses glycogen from sloughed epithelial cells, converting it into glucose which in turn is metabolised to lactic acid thereby creating a mildly acidic vaginal environment which in turn discourages the growth of pathogenic microorganisms (Goldstein I and Alexander JL. 2005).

As oestrogen levels start to decline, key physiological changes that occur in the vagina/vulva area include thinning of the vaginal epithelium, an increase in vaginal pH (from mildly acidic to neutral and alkaline) and a decrease of approximately 30% of type I & Type II collagen in the vaginal tissue during the first few years following menopause (Brincat et al., 1985; Affinito et al., 1999; Sodeberg et al., 2009) This results in a gradual relaxation of the connective tissue support structure which leads into a general decline in the structure and tone of the genital area (Affinito et al., 1999).Thinning of the epithelial layer leads to increased friability and lowered elasticity of vaginal tissues.

As the physiological changes gradually occur in the genital structure and function, vaginal and vulva atrophy increases. Atrophy of the vaginal epithelia, vascular muscular and connective tissue causes the vaginal vault to become pale or colourless with resulting loss of multiple folds or rugae that are present in a rich oestrogen environment. Associated atrophy of the lamina propria blood vessels reduce blood flow to the tissues. This in turn results in a decrease in natural lubrication resulting in vaginal dryness with the severity of dryness increasing over time from menopause. The endocervical glandular tissue also produces less mucin, which further contributes to vaginal dryness (Goldstein I and Alexander JL. 2005).

Vaginal dryness or decreased vaginal lubrication is a symptom generally associated with menopause / post menopause and publications on vaginal dryness tend to focus on women in the menopause / postmenopausal phase (Palacios S, 2014; Panay N and Fenton A, 2014). Vaginal dryness, however, may occur in all ages. Approximately 15% of pre-menopausal and up to 57% of post-menopausal women experience symptoms of urogenital atrophy of which vaginal dryness is a symptom (Goldstein I and Alexander JL. 2005). Vaginal dryness in premenopausal women can be permanent or transient due to several reasons e.g. prolonged periods of low oestrogens such as post pregnancy and breast feeding (Davies et al., 2004), low dose combined oral contraceptive and or progestogen-only methods (Basson et al., 2005), smoking (Kalogeraki et al., 1996), vaginal nulliparity, medications to decrease oestrogen levels, some health conditions (Leiblum et al., 1983) and other potential contact and irritant factors to the vaginal mucosa resembling symptoms of

atrophic vaginitis (Bachmann G and Nevadunsky NS, 2000). Vaginal dryness may also occur after surgery to the uterus or ovaries (Nappi et al., 2012), during some metabolic disorders, stress, obesity (by increasing vaginal infections and worsening vaginal discharge aggravates symptoms of Vaginal/Vulva Atrophy (VVA)), diabetes (Pastore et al., 2004) and following cancer therapy (Couzi et al., 1995).

The gradual decline in oestrogen production is accompanied by common menopausal vasomotor symptoms including hot flushes, menstrual irregularities, night sweats, insomnia, headaches, anxiety, dizziness, depression, irritability, gastrointestinal upset and urinary difficulties which eventually resolve with time (Bachmann G and Nevadunsky NS, 2000; Greendale GA and Judd HL, 1993). Urogenital symptoms which include a decrease in vaginal lubrication, however, increases in prevalence and therefore, unlikely to improve overtime without treatment and if treatment discontinues the symptoms return (Dennerstein et al., 2000).

The symptoms of VVA can and do have a significant negative impact on interpersonal relationships, quality of life (QoL), daily activities such as walking or exercising which creates genital discomfort (Nappi et al., 2014). Studies have reported the marked effect it has on sexual activity and QoL which is discussed below.

Physiologically, the female sexual response cycle is initiated by neurotransmitter-medicated vascular and non-vascular smooth muscle relaxation which results in an increased pelvic blood flow, vaginal lubrication and both clitoral and labial engorgement. These events are orchestrated through a combination of neuromuscular and vasocongestive mechanisms. Any physiologic impairment that interferes with this cycle will affect sexual arousal, vaginal lubrication, genital sensation and the ability to achieve orgasm (Berman et al., 2000). Oestrogen plays a key role in maintaining a balanced vaginal environment throughout the productive years, however, as the levels of oestrogen declines the resulting VVA increases together with the associated decrease in vaginal lubrication i.e. increase in vaginal dryness and dyspareunia. Continued vaginal dryness often leads to difficulties with sexual arousal, pruritus, dysuria, burning, purulent and malodorous discharge in addition to other sexual and non - sexual complaints (Sarrel PM, 1987; Macoy et al., 1985) which can therefore lead to loss of sexual desire or emotional and interpersonal difficulties (Shearer et al., 1977; Easley EB, 1978).

Unlike many other menopausal symptoms, vaginal dryness increases over time and with age. Over 72% of women in their seventh decade may report inadequate vaginal moisture with up to two thirds of postmenopausal women associating their complaint of dyspareunia with vaginal dryness (Sarrel PM, 1987). As highlighted, symptoms of VVA can and do have a significant negative impact on sexual function. The Real Women's Views of Treatment Options for Menopausal Vaginal Changes (REVIVE) survey conducted in 3046 postmenopausal women in the United States (US) highlighted the most common VVA symptoms to be dryness (55%), dyspareunia (44%) and irritation (37%) which affected enjoyment of sex in over half (59%) of the participants (Kingsberg et al., 2013). Other studies have highlighted that vaginal dryness affects their sexual activity and QoL (Stenberg et al., 1996). The results of these and other similar studies reinforces the fact that many women perceive vaginal dryness and discomfort as having a substantial negative impact on their

lives and in particular with respect to their sexual intimacy, their ability to have a loving relationship and an overall QoL (Simon et al., 2013).

As a woman travels through pre-menopause, menopause and post-menopausal phases in her life, it is accompanied by physiological and emotional changes, sometimes accompanied by health issues which together, will have an impact on her QoL. Vaginal dryness is a key factor that has a significant impact on QoL as it can affect normal everyday activities and can have a major impact on sexual activity, to the point that it can lead to increasing hostility and dissatisfaction, decreasing frequency of sexual encounters, pain with coitus and increased symptoms of poor vaginal health. Sexual activity is a healthy prescription for postmenopausal women (Easley EB, 1978) as it has been shown to encourage vaginal elasticity and pliability with lubrication. Studies have shown that women with VVA have no coital discomfort as long as they are engaging in regular intercourse; abstinence from coital activity has been associated with progressive shrinkage of the vagina (Leiblum et al. 1983; Notelovitz M, 1978). It is necessary, therefore, to address vaginal dryness in order to create a balanced vaginal microenvironment that can support a better QoL.

Treatment options for VVA consist of prescription e.g. systemic hormone replacement therapy (HRT), vaginal oestrogen products and over-the-counter non-hormone lubricants and moisturisers with the choice of therapy dependent of the severity of the symptoms, effectiveness and safety of the therapy for the individual patient and patient preference. Many women decline the use of hormone based estrogenic products for several reasons including side effects associated with oestrogens therapy e.g. breast tenderness, resumption of menstrual cycle or personal preferences (Semmens et al., 1985). Hormone therapy is also contraindicated under several conditions e.g. women with a history of cancer or thromboembolism. Many women choose not to use hormone-based products due to the safety concerns raised in the aftermath of the women's health initiative (Rossouw et al., 2002). The concerns led the Food and Drug Administration (FDA) to make changes in the labelling of hormone therapy defining clearly that its use in the treatment of moderate to severe vasomotor symptoms is the primary indication. This relabelling reduces the treatment options available especially for several groups of women i.e. older women with VVA who no longer complain of vasomotor symptoms, for women who prefer oral over vaginal treatment and women who want to avoid the use of oestrogen due to side effects or contraindications.

The Endocrine Society Clinical Practice Guideline suggests that personal lubricants are recommended for those who produce insufficient vaginal secretions to allow for comfortable sexual activity (Steunkel CA et al., 2015). Additionally, the American Society of Clinical Oncology, Inc. (ASCO) and Cancer Care Ontario (CCO) also recommend lubricants for all sexual activity or touch as part of first-line treatment for mild to moderate symptoms of VVA (Carter et al., 2018).

[redacted]

[redacted] To comply with the MDR, two personal lubricants, [redacted], will be investigated.

1.2 Investigational Product

The investigational products (IPs), [redacted], are personal vaginal lubricants [redacted] The IPs come in contact with vaginal and vulval skin / mucosa each time it is used. The lubricants are for short-term use and contact is unlikely to exceed 24 hours. The IP can be applied up to 4 times per day.

[redacted]

A comparator, in the form of a non-sensate water-based lubricant and a non-sensate silicone-based lubricant, will be included as part of the oral assessment in the Tolerance Phase for comparison with [redacted], respectively.

The lubricants to be used in this clinical investigation have been manufactured to Good Manufacturing Practice (GMP) requirements as per International Organisation for Standardisation (ISO) 13485 Medical device – Quality management system – Requirement for regulatory purposes.

1.3 Treatment Rationale

The proposed clinical investigation is a parallel-design investigation to determine the effectiveness and safety of one water-based personal lubricant and one silicone-based personal lubricant for the relief of intimate discomfort associated with vaginal dryness. [redacted]

The clinical investigation will include two phases: the Tolerance Phase, followed by the Treatment Phase (use-as-intended phase).

During the Tolerance Phase, a pea-sized amount of IP and comparator will be used for oral assessment and a 3 g of IP will be used for gynaecological assessments. The effects of the IPs on vulvovaginal and oral mucosal tissues, [redacted] will be assessed to verify the safety of the IPs for their intended purpose. This phase will be carried out in the clinical setting to allow objective assessments by the investigator (gynaecologist and dermatologist), although the subjects will be asked to complete questions relating to their perception of the tolerability of [redacted] on vulvovaginal and oral mucosal tissues.

Use of a comparator was deemed necessary for the oral mucosal assessment to further assess the difference, if any, in the subjects' perception of the test lubricants with sensory effects, as compared to the comparator without the sensory effect. The investigator (dermatologist) carrying out the oral mucosal assessment will also note any differences during the assessment.

The use-as-intended phase will be mainly based at home, with subjects using the lubricant during each sex occasion and recording the use of the product in their diaries. Subjects will engage in vaginal penetrative sex at least once per week (or twice per week to account for a menstrual period break) over a 4-week period but will not be prohibited from engaging in other forms of sexual activity (e.g. receptive oral/anal sex, non-penetrative and penetrative masturbation with a sex toy, partner's fingers or solo). Subjects will not be prohibited from using condoms, but this will not be the only form of contraception and the use will be captured in the diary. This will ensure that the subjects are not changing their routine to the extent that the participation in the clinical investigation is significantly interfering with their normal life and that the conditions of the clinical study are as close to real life as possible.

According to the Biological Safety Risk Assessment (BSRA) carried out on the two IPs [redacted] under normal use during sex, a single application of 3 g of product once per day is likely to be used per partner [redacted] Hence, for the purpose of this clinical investigation, during the tolerance (vulvovaginal assessment) and treatment phase, an approximately 3 g amount of lubricant will be considered 1 application. Subjects will be provided with a demonstration of a dispensed 3 g amount for reference. The IP can be applied up to 4 times per day.

1.4 Investigation Population and Indication

[redacted] Thus, the investigation population will include female subjects meeting the inclusion and exclusion criteria who experience discomfort associated with vaginal dryness during sexual intercourse. Prior lubricant use will not be a factor and as such, investigation population will include subjects regardless of lubricant use. As lubricants are used by women of varying ages, the study population will include an approximate 1:1 ratio of pre-menopausal to post-menopausal, with a difference of up to 40:60 (up to a maximum of 60% in either sub-population) being allowed to ensure a population representative of the general lubricant user population is considered. To ensure the

ratio of pre-menopausal and post-menopausal women is the same in both treatment groups, the randomisation schedule will be stratified by menopausal status.

Due to the exposure of the male partner to the IPs, inclusion of the subject into the investigation will require consent from both female and male partner. Safety and efficacy endpoints (AEs and questionnaires) will be evaluated for the male partner during the Treatment Phase. Except Section 8 of this clinical investigation plan (CIP), where the term of "subject" refers to both female and male partners, female participant is referred to as the subject. Information on the activities undertaken by the male partner is specifically noted and also summarised in Section 6.2.

1.5 Non-Clinical Evidence

[redacted]

1.6 Clinical Evidence to Date

[redacted]

1.6.1 Clinical in-use investigation on [redacted]

[redacted]

[redacted]

1.6.2 Acute tolerance study on [redacted]

[redacted]

1.6.3 Post-marketing adverse event surveillance data [redacted]

[redacted]

[redacted]

1.6.4 Summary of adverse events from literature

[redacted]

1.7 Benefits / Risks Assessment

This investigation has been designed to evaluate the effectiveness and safety of two personal vaginal lubricants: [redacted] Subjects in this investigation are females who experience intimate discomfort associated with vaginal dryness during sexual intercourse. Such investigational population are expected to experience a level of relief from intimate discomfort during sexual intercourse with the use of their allocated IP.

Additionally, each subject will undergo a physical examination, including a gynaecological examination as part of enrolment into the investigation to confirm that the subject is sexually healthy as defined in this investigation. The examination is a standard gynaecological examination, however due to the indication of vaginal dryness, the examination may be unpleasant or painful depending on the severity of the subject's symptoms. Slight bleeding due to injury to the skin may occur when inserting the speculum. Subjects with underlying conditions identified though the physical examination will be referred as appropriate. [redacted]

Only those subjects who meet the eligibility criteria set out in this investigation, and as assessed by the Investigator as being suitable to enter into the investigation will be enrolled. Subjects of childbearing potential will be required to be on a highly effective form of contraception before being enrolled into the investigation, additionally subjects will be screened for sexually transmitted infection (STI), however in the event that the subject become pregnant or contracts an STI they will have access to the clinical site where appropriate follow-up measures will be taken.

[redacted]

subjects who experience any untoward medical occurrence during the investigation have access to the Investigator/clinical site where appropriate measures will be taken. Additionally, the Investigator (in consultation with the gynaecologist) will determine if a subject remains eligible to move into the Treatment Phase of the investigation after the completion of the Tolerance Phase, as per the inclusion/exclusion criteria and provided that the subject has not experienced any untoward medical occurrence.

[redacted]

Female subjects or their partner who has previously experienced an irritant or allergic reaction to any personal lubricant, vaginal moisturiser or female hygiene product or known to have any hypersensitivity to the test product ingredients will be excluded from the study, and the subjects will be instructed to stop use and seek medical attention in any instance of irritation. Subjects and their male partners will also be excluded if they report broken skin or wounds in the intimate area. The investigation includes safety measures expected of a personal lubricant study and therefore, the overall benefit-risk profile for the use of the IPs as defined in this CIP is considered acceptable.

1.7.1 Covid-19

For subjects, all mandated hygiene measures and social distancing requirements will be followed in line with government guidelines and all relevant local guidelines which will be monitored throughout the course of the clinical investigation and any changes will be implemented as the clinical investigation progresses. Procedures required to be followed by subjects will be documented in the site file.

If required per local regulation, subjects will be provided with additional information about COVID-19 and any additional requirements in relation to their participation. This information will be provided to subjects in written and verbal format and they will be asked to sign that they have understood this additional information before proceeding with their involvement in the clinical investigation. Subjects will be reminded that they can discontinue participation and withdraw their informed consent at any time.

The risk-benefit analysis for this investigation has been performed to consider the potential impact of COVID-19 on the safety and wellbeing of subjects and on the potential for the clinical investigation to be conducted appropriately. Risk assessments will be revisited throughout the course of the clinical investigation and input from the Investigator(s) will be used to identify the current local risk to the clinical investigation and those at the site.

1.8 Ethical Conduct of the Investigation

This investigation will be conducted in accordance with this CIP and the principles set out in the Declaration of Helsinki. It will comply with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), ISO 14155:2020 and applicable regulatory requirements.

2 INVESTIGATION OBJECTIVES AND ENDPOINTS

2.1 Investigation Objectives and Endpoints

The investigation endpoints based on the investigation objectives are provided in Table 2-1.

Table 2-1 Investigation Objectives and Endpoints

Treatment Phase	
Primary Objective	**Endpoints**
To demonstrate the effectiveness of two personal lubricants when used as intended during vaginal intercourse in women who experience intimate discomfort associated with vaginal dryness.	Primary endpoint: Total Female Sexual Function Index (FSFI) score – change from baseline in total FSFI score at least 4 (≥4) points at 4 weeks of use of two personal lubricants. Secondary endpoints: • Number and percentage of subjects who achieve at least 4-point (≥4) increase in total FSFI between baseline and 4 weeks. • Number and percentage of subjects who transition from sexual dysfunction (≤26.55 total FSFI score) to sexual function (>26.55 total FSFI score) between baseline and 4 weeks. • Change from baseline in individual domain scores (Pain, Lubrication, Desire, Arousal, Satisfaction, Orgasm) at 4 weeks.
Secondary Objectives	**Secondary Endpoints**
To assess subject's perception of two personal lubricants when used during vaginal intercourse in women who experience intimate discomfort associated with vaginal dryness.	The subjects' perception of two personal lubricants determined through Subject Perceived Questionnaire (SPQ) after first product use (within 24 hours of intercourse) and at 4 weeks.

To assess subject's global evaluation of two personal lubricants when used during vaginal intercourse in women who experience intimate discomfort associated with vaginal dryness.	Subject Global Evaluation of product effectiveness, tolerability, and device usability (included in the SPQ) at 4 weeks.
To assess male partner's perception of two personal lubricants when used during vaginal intercourse.	The male partner's perception of two personal lubricants determined through Subject Perceived Questionnaire (SPQ) after first product use (within 24 hours of intercourse) and at 4 weeks.
To assess the effects of two personal lubricants on the impression of change in the sexual intimacy between female subjects and their male partners.	• Number and percentage of female subjects recording ≥2 improvement in sexual intimacy on the Patient Global Impression of Chang (PGIC) at 4 weeks. • Number and percentage of male partners recording ≥2 improvement in sexual intimacy on the PGIC at 4 weeks.
Tolerance Phase	
Secondary Objectives	**Secondary Endpoints**
To assess vulvovaginal tolerance of two personal lubricants in women who experience intimate discomfort associated with vaginal dryness.	• An assessment of the Vaginal Epithelial Tolerability (VET) of the two personal lubricants at baseline, 2 and 24 hours post single application as assessed by gynaecologist examination. • Subject Perception of Vulvovaginal Tolerance of the two personal lubricants will be determined through Subject Perceived Questions at 24 hours post single application. • A Global Assessment of Vulvovaginal Tolerance for each subject at 24 hours post single application as determined by the gynaecologist. • Overall Vulvovaginal Tolerance Rating Statement for each personal lubricant as determined by the gynaecologist.
To assess oral mucosal tolerance of two personal lubricants in women who experience	• An assessment of the Oral Mucosal Tolerance of the personal lubricants at

intimate discomfort associated with vaginal dryness.	baseline, 30 minutes, 2 and 24 hours post single application to the upper and lower inner lip as assessed by dermatologist. • Subject Perception of Oral Mucosal Tolerance of the two personal lubricants will be determined through Subject Perceived Questions at 24 hours post single application. • Global Assessment of Oral Mucosal Tolerance for each subject at 24 hours post single application as determined by the dermatologist. • Overall Oral Mucosal Tolerance Rating Statement for each personal lubricant as determined by the dermatologist.
[redacted]	
Tolerance Phase and Treatment Phase	
Safety Objective	**Safety Endpoint**
To assess the safety and establish the safety profile of two personal lubricants in women who experience intimate discomfort associated with vaginal dryness.	Overall proportion of subjects with Adverse Events/Adverse Device Effects (AE/ADEs) i.e. the occurrence of one of more AE/ADE per subject.
To assess the safety and establish the safety profile of two personal lubricants in males.	Overall proportion of males with Adverse Events/Adverse Device Effects (AE/ADEs) i.e. the occurrence of one of more AE/ADE per male partner.
[redacted]	

[redacted]	[redacted]

2.2 Success Criteria

Observation of a statistically significant and clinically important change from baseline in total FSFI score at 4 weeks. A pre-specified minimum clinically important difference (MCID) is +4 points from baseline to 4 weeks. The MCID of +4 points is based on two previous studies (Krychman et al., 2017; DeRogatis et al., 2014), and from discussions with Key Opinion Leaders. Krychman et al. (2017) concluded that in a study of 186 women with vaginal laxity randomised to receive either surface-cooled radiofrequency therapy or placebo, the MCID for the FSFI total score over a 6-month intervention period was an improvement of at least 4.8 points. The MCID was derived based on the proportion of subjects who experienced what they perceived to be a clinically meaningful treatment benefit relative to the change in total FSFI score. In another study (DeRogatis et al., 2014), which evaluated the efficacy of bremelanotide in 397 women with hypoactive sexual desire disorder and female sexual arousal disorder, the MCID for the FSFI total score was pre-defined as an improvement of at least 4 points, over a 6-month intervention period. Whilst the current study is over a shorter period (4-week treatment) and is not in a cohort of women with a female sexual dysfunction diagnosis, a change of +4 points in total FSFI score is considered relevant and is consistent with previous studies utilising the FSFI.

3 INVESTIGATION DESIGN AND RATIONALE FOR DESIGN

3.1 Investigation Design

This is a two-arm, parallel-design investigation to determine the effectiveness and safety of two personal lubricants. This investigation consists of two phases, a Tolerance Phase and a Treatment Phase. Following the screening visit, a subset of subjects will enter the Tolerance Phase and upon completion, will then enter the Treatment Phase. The remaining subjects will enter the Treatment phase only, following the screening visit. The investigation population involve pre- and post-menopausal women, and this investigation has been stratified by menopausal status. All subjects will attend a screening visit, to assess subject eligibility. Eligible subjects will either enter the Tolerance Phase or the Treatment Phase.

The Tolerance Phase consists of a 7-day washout period followed by two further visits. At visit 2, subjects will undergo the oral mucosal tolerance assessment carried out by the dermatologist at baseline, 30 minutes, and 2 hours after a single application of their allocated IP and the respective comparator. In addition to the oral mucosal tolerance assessment, subjects will undergo the vulvovaginal tolerance assessment carried out by the gynaecologist at baseline and 2 hours after a single application of their allocated IP. Upon completion of these assessments, subjects can leave the clinical site. Subjects will return to the clinical site for Visit 3 where oral mucosal tolerance assessment and vulvovaginal tolerance assessment will be performed 24 hours post single

application. At the end of the Tolerance Phase, the investigator, in consultation with the gynaecologist and the dermatologist, will determine whether subjects remain eligible to enter the Treatment Phase of the investigation.

The Treatment Phase consists of a 4-week run-in phase followed by two further visits. At Visit 2, baseline assessment will be taken, after which subjects will be provided with their allocated IP to use at least once a week over a 4-week period. At Visit 3, clinical assessments will be performed following 4-week product use. There after couple's involvement in the clinical investigation will be complete.

Based on the anticipated safety profile of IPs and comparators (see IB for further information), there are no significant concerns regarding their tolerability and safety. The investigation therefore does not require the Tolerance Phase to precede the Treatment Phase, and the two phases will be run in parallel.

3.2 Rationale for Investigation Design

The proposed investigation has been designed to demonstrate the effectiveness and in-use tolerability of two personal lubricants for the relief of intimate discomfort associated with vaginal dryness (the intended purpose of these lubricants). The investigation will recruit female subjects who experience discomfort during sexual intercourse. The subject population will include both pre- and post-menopausal women in a sexually active heterosexual relationship.

A two-arm, parallel design, clinical investigation is proposed to demonstrate that two personal lubricants are safe and effective for their intended purpose and are well tolerated by the vaginal epithelium and oral mucosa. A parallel design has been selected as there is no intention to formally compare the test products. For registration and compliance purposes, the safety and effectiveness of the products for their primary medical intended purpose must be demonstrated clinically, and this design is suitable to do so.

The investigation will include two phases: the Tolerance Phase, followed by the Treatment Phase. Following penetrative sex, the vaginal epithelium can present with the markers for irritation such as redness and swelling which will interfere with assessing the product effect on the vaginal epithelium. For this reason, the Tolerance Phase has been separated from the Treatment Phase to ensure a focussed assessment of each product's effect on the vaginal epithelium.

Only a subset of subjects will participate in the Tolerance Phase. This means that some subjects will start the investigation in the Tolerance Phase, followed by the Treatment Phase. Other subjects will start the investigation in the Treatment Phase.

The Tolerance Phase will consist of the vulvovaginal and oral mucosal tolerance assessments, [redacted] The purpose of the oral mucosal tolerance

assessment is to generate clinical data to further support the safety of the lubricants for oral sex. Another reason is to evaluate subjects' perception of oral tolerance (as opposed to the objective assessment of oral tolerance carried out by the dermatologist) to the IPs, specifically the ingredients responsible for the sensory action within each formulation. In addition, a comparison between oral mucosal tolerance and vulvovaginal tolerance for each subject and between subjects will highlight intra- and inter- subject trends in oral and vulvovaginal response to the sensate agents. A comparator in the form of a non-sensate water-based lubricant and a non-sensate silicone-based lubricant, will be included as part of this oral assessment for comparison with [redacted] respectively. The purpose of the comparator is to further compare objective and subjective response to the IPs containing sensory agents as opposed to lubricants that do not contain sensory agents.

[redacted] Table 3-1 outlines which IPs are tested in each phase/tolerance assessment and whether a comparator is used alongside the IP.

Due to the exposure of the male partner to the IPs, inclusion of the subject into the investigation will require consent from both female and male partner. Safety and efficacy endpoints (AEs and questionnaires) will be evaluated for the male partner during the Treatment Phase.

Table 3-1 IPs and Comparators Tested in Each Phase/Tolerance Assessment

IP/Comparator used	Clinical Investigation Phase			
	Tolerance Phase			Treatment Phase
	Vulvovaginal Tolerance Assessment	Oral Mucosal Tolerance Assessment	[redacted]	
[redacted]	✓	✓		✓
[redacted]	✓	✓		✓
Comparators (non-sensate water-based lubricant or non-sensate silicone-based lubricant)		✓		

3.3 Determination of Sample Size

Based on 2 previous studies (Krychman et al., 2017; DeRogatis et al., 2014), and from discussions with Key Opinion Leaders, a change of 4 in the Total FSFI score can be considered a minimal

clinically important change from baseline. [redacted] taking into account the adjustment required to the significance level for testing 2 primary treatment comparisons, the study would require 24 subjects completing the 4-week treatment period in each of the 2 treatment groups. A study of this size would have 90% power for assessment of the primary endpoint. The individual FSFI domains are also of key importance in this study. [redacted]

For the study to be sufficiently powered for the primary endpoint and the individual FSFI domains, 33 subjects will be randomised to each treatment group, which allows for a 10% attrition rate.

A subset of 22 subjects will be selected in a 1:1 treatment ratio (see Section 6.3) to participate in the Tolerance Phase of the investigation, undergoing vulvovaginal and oral mucosal assessments, [redacted]. Allowing for a 10% attrition rate this should ensure 20 subjects complete the Tolerance Phase. They will then move into the Treatment Phase, whereas the rest of the subjects in each arm will participate in the Treatment Phase only.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Investigation Population

A sufficient number of pre- and post-menopausal women will be screened from the clinical site's database and / or through advertising to the public.

66 subjects having provided informed consent and who meet the eligibility criteria will be randomised into the investigation to ensure 30 subjects per treatment group complete the investigation.

The investigation population will include an approximate 1:1 ratio of pre- and post-menopausal women for both tolerance and treatment period per IP, with a difference of up to 40:60 split.

There will be 1 clinical site in Germany participating in the investigation.

4.2 Inclusion Criteria

The inclusion criteria comprise criterions which are applicable for all subjects (pre- and post-menopausal) as well as additional criterions exclusive to each sub-population. Only subjects to whom all the following conditions apply will be included.

4.2.1 Universal Inclusion Criteria

1. Subject and their male partner have provided written informed consent.
2. Subject is female and both subject and their male partner are aged at least 18 years. Maximum age of female subject is 65 years.

3. Subject and their male partner in a mutually monogamous heterosexual relationship (≥ 3 months) who are sexually active, defined as having sexual intercourse at least once a week. (Note: The number of sexual intercourses may comprise twice in one week to account for a menstrual period break.)
4. Female subject that agrees to have a gynaecological pelvic examination to ensure no significant disease findings and have intact skin and mucous in the test region (vaginal and vulvar / intimate area) except skin dryness as visually assessed by the gynaecologist at all the relevant time points.
5. Female subject that agrees to an oral exam by a dermatologist to ensure no significant disease findings and have intact skin and mucous in the test region (oral cavity - including lips, inside lining of the lips, cheeks (buccal mucosa), teeth, gums, tongue, the floor of the mouth, roof of the mouth (hard palate) and area behind wisdom teeth (retromolar trigone).
6. Subjects reporting mild to moderate vaginal dryness and dyspareunia during sex (when not using lubricant) in the past 3 months as confirmed by a score of 1 or 2 for vaginal dryness and 1 or 2 for dyspareunia on the Verbal Rating Scale (VRS) of dyspareunia and vaginal dryness.

4.2.2 Pre-menopausal Inclusion Criteria

1. Female of childbearing potential who is willing to use a highly effective method of contraception throughout the clinical investigation. A female is considered to be of childbearing potential following menarche and until becoming post-menopausal unless permanently sterile by methods including hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A highly effective method of contraception is defined as a method that can achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods include combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal and transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable and implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner (who has received medical assessment of the surgical success)(Recommendations related to contraception and pregnancy testing in clinical trials, Clinical Trials Facilitation and Coordination Group, Version 1.1, 2020).

4.2.3 Post-menopausal Inclusion Criteria

1. Female subject in post-menopausal phase defined as having amenorrhea (absence of menstruation) for at least 12 consecutive months without an alternative medical cause (Recommendations related to contraception and pregnancy testing in clinical trials, Clinical Trials Facilitation and Coordination Group, Version 1.1, 2020).
2. Female subject with premature menopause – due to surgical menopause or physiological menopause within the last 12 consecutive months of the screening visit (diagnosis to be confirmed as irreversible in subjects' medical history) or after having received chemotherapy.

4.3 Exclusion Criteria

The exclusion criteria comprise criterions which are applicable for all subjects (pre- and post-menopausal) as well as additional criterions exclusive to each sub-population. Subjects to whom any of the following conditions apply must be excluded.

4.3.1 Universal Exclusion Criteria

1. Female subject or their partner who has previously experienced an irritant or allergic reaction to any personal lubricant, vaginal moisturiser or female hygiene product or known to have any contact allergy or allergy/ hypersensitivity to the test product ingredients.
2. Female subject with history of mucosal intolerance to warming agents.
3. Female subject with continuous or intermittent oral allergy syndrome or burning mouth syndrome, or history of thereof (self-reported).
4. Female subject with urinary, vaginal infection (fungal, bacterial) or sexually transmitted infection at screening visit, which in the opinion of the investigator would affect the study outcomes or the safety of the subject.
5. Female subject that has any condition of the oral cavity, including oral infection, active oral herpes simplex virus, active canker sores or oral ulcers and erosions as determined by the investigator.
6. Female subject who has had a positive cervical screening examination for human papillomavirus (HPV) within the 3 years of the screening visit (medical history/self-reported).
7. Female subject presenting with signs of internal irritation, active psoriasis, lichen sclerosis, eczema or other active skin disorder upon clinical examination.
8. Male partner of female subjects has broken skin or wounds in the intimate area (self-reported).
9. Female subject with a history of skin disorder, which in the opinion of the investigator will affect study outcome.
10. Female subject presenting clinically abnormal findings other than irritation e.g. lumps, open sores or blister type wounds during the physical examination (including the gynaecological examination) that in the opinion of the investigator will affect study outcome.
11. Female subject that has had a suspicion of malignancy or history of malignancy within the past 2 years (self-reported).
12. Female subject with autoimmune conditions or any medical conditions which in the opinion of the investigator could compromise the immune function.
13. Female subject who has had surgical cervical excision or vaginal and/or vulvar procedures, including laser and cosmetic procedures to the vulva or vagina in the previous year.
14. Female subject that has any tooth ache or other dental/oral malady (self- reported).
15. Female subject with ongoing dental/orthodontic procedures or any medical/surgical interventions involving the oral cavity (self-reported).

16. Female subject currently being treated with systemic medications or medicines (e.g. glucocorticosteroids, antibiotics, local oestrogen and other intravaginal products) that are acting locally in the vaginal area which may influence the clinical study outcomes.
17. Female subject who has started, stopped, or changed hormonal treatments (for contraception, vaginal dryness, or any other condition) during the previous 3 months prior to screening or those intending or expecting a change in treatment during the investigation.
18. Female subject who has used any kind of topical histamine and/or topical hormonal based product in the form of an intravaginal cream or moisturiser for local treatment of vaginal dryness in the past 3 months.
19. Female subject taking steroid preparations, immunosuppressants or any other medication which in the opinion of the investigator may affect the test results:
    a. Anti-inflammatory or antihistamine within 1 week prior to the screening visit
    b. Cough suppressants or corticosteroids within 4 weeks prior to screening visit.
    c. Retinoids or immune suppressants within 6 months prior to screening visits.
20. Female subject who has had any change to medication or treatment regimen for the treatment of diabetes mellitus during the previous 3 months prior to screening.
21. Female subject using non-medicated, over the counter product, herbal/natural remedies on the vulva, vaginal opening and inside the vagina and is unwilling to stop at least 7 days prior to screening and throughout the duration of clinical investigation.
22. Female subject showing vaginal prolapse and/or other medical conditions that could interfere with the investigation conduct and participation.
23. Female subject using vaginal douches and is unwilling to stop its use at least 2 weeks prior to screening and throughout the duration of the clinical investigation.
24. Female subject or their male partner that, in the opinion of the investigator, will be unable to comply fully with the study requirements or unable to tolerate the procedures described in the CIP.
25. Female subject has participated in another investigation where a medicinal, medical device clinical investigation or any form of studies involved testing on female intimate area within 3 months prior to screening.
26. Female subject or their male partner has received an investigational product or participated in another trial involving a marketed or investigational drug in the 30 days (or for investigational agents with a long half-life, a washout of 5 half-lives) prior to screening. Or if the investigator believes that any previous participation in an investigational study would be to the detriment of the safety of the participant or the conduct of the study.
27. Female subject or their male partner who is an employee at the site or a partner or first-degree relative of the Investigator.
28. Female subject or their male partner fails to satisfy the investigator of fitness to participate for any other reason.

4.3.2 Pre-menopausal Exclusion Criteria

1. Female subject who is pregnant (as confirmed by a positive pregnancy test), breast-feeding or trying to conceive.

4.3.3 Post-menopausal Exclusion Criteria

1. Female subject that has had previous episodes of vaginal bleeding of unknown origin within the last 6 months of the screening visit.

4.3.4 Tolerance Subset - Exclusion Criteria for Enrolling into Treatment Phase

Subjects participating in the Tolerance Phase who have any of the following conditions must not continue to the Treatment Phase.

1. Any observed severe irritancy reactions at any time point.
2. Any reaction failing to adequately resolve or needing further treatment, that in the opinion of the investigator represents an unacceptable risk to proceed with the investigation.
3. Any AEs considered related to the investigational product that are serious and/or severe in nature that in the opinion of the investigator represent an unacceptable risk to proceed with the investigation.

4.4 Investigation Restrictions

4.4.1 Dietary and Lifestyle Restrictions

Dietary and Lifestyle restrictions for subjects and male partners are listed in Table 4-1 below:

Table 4-1 Dietary and Lifestyle Restrictions

Restriction	From	To	Applicable to female subjects	Applicable to male partners
Tolerance Phase and Treatment Phase				
Subjects are not permitted to use personal lubricant compounds other than the investigational product.	Screening	End of investigation	Yes	Yes
Subjects are not permitted to apply any products for the relief of vaginal dryness, other than the investigational product.	Screening	End of investigation	Yes	No

Restriction	From	To	Applicable to female subjects	Applicable to male partners
Subjects are not permitted to use their usual personal lubricants or remedies for vaginal dryness.	Screening	End of investigation	Yes	No
Subjects are not permitted to use any topical products on the intimate area.	Screening	End of investigation	Yes	Yes
Subjects should not change any topical skin product(s). (For use of topical products in the intimate area – see other restrictions.)	Screening	End of investigation	Yes	Yes
If bathing, subjects must not remain too long (longer than 10-15 minutes) in the water and not to use bath additives such as bath salts, bath oils etc.	Screening	End of investigation	Yes	Yes
Subjects are not permitted to change from their usual brand of sanitary products.	Screening	End of investigation	Yes	Yes
Subjects are not permitted to change the fabric detergent or fabric softener for clothes.	Screening	End of investigation	Yes	Yes
Subjects are not permitted to swim or bathe in chlorinated pool/spa or use jacuzzi tubs.	Screening	End of investigation	Yes	Yes
Subjects are not permitted to use washing implements such as wash cloths to wash the intimate area – only use hands.	Screening	End of investigation	Yes	Yes
Tolerance Phase				
Pre-menopausal women are not permitted to use tampons.	Screening	End of Tolerance Phase	Yes	No

Restriction	From	To	Applicable to female subjects	Applicable to male partners
Subjects are not permitted to use hygiene products or personal intimate grooming products in the intimate area (e.g. use of intimate washes, waxes, razor blade etc.) only water to be used in the intimate area.	Screening	End of Tolerance Phase	Yes	No
Subjects are to refrain from engaging in vaginal sex or any other vaginal penetrative sexual activity e.g. digital stimulation or use of sex toys.	Screening	End of Tolerance Phase	Yes	No
Subjects are not permitted to use any new oral products that are irregular to their normal dental hygiene routine or eating any new foods outside their normal diet.	Screening	End of Tolerance Phase	Yes	No
Treatment Phase				
No change in use of personal intimate hygiene products or personal intimate grooming products e.g. intimate washes, waxes, razor blade etc.	Screening (or End of Tolerance Phase for the tolerance subset)	End of investigation	Yes	Yes

4.4.2 General Restrictions

General investigation restrictions for subjects and male partners are listed in Table 4-2 below:

Table 4-2 General Restrictions

Restriction	From	To	Applicable to female subjects	Applicable to male partners

Avoid unprotected sexual intercourse for female subjects of childbearing potential.	28 days prior to Screening	End of investigation	Yes	No
Enrolment into another clinical investigation/study once participating in this investigation.	Screening	End of investigation	Yes	Yes
A change of partner.	Screening	End of investigation	Yes	Yes

4.5 Discontinuation / Withdrawal and Replacement of Subjects

The Investigator may withdraw the subject from the investigation at any time. Reasons for removing a subject from the investigation include, but are not limited to:

- AEs that in the judgement of the Investigator may cause severe or permanent harm (significant clinical deterioration is an AE)
- Violation of the CIP, which in the judgement of the Investigator affects subject's/male partner's safety or data integrity
- In the Investigator's judgement, it is in the subject's/male partner's best interest (this includes inadequate device performance)
- Subject/Male partner declines further investigation participation

The primary reason for withdrawal will be documented in the electronic case report form (eCRF).

For subjects who are lost to follow-up, at least 2 documented attempts should be made to contact the subjects for follow-up assessments which will include assessments as described for Visit 3 of the Tolerance Phase (Section 7.3.3) or Visit 3 of the Treatment Phase (Section 7.4.3).

30 subjects per treatment group are required to complete the 4-week Treatment Phase. A subset of 20 subjects is required to complete the Tolerance Phase. Subjects who withdraw from the investigation before receiving any IP will be replaced.

5 INVESTIGATION TREATMENT

5.1 Medical Device

The following IPs will be evaluated in this investigation:

- IP A: [redacted]
- IP B: [redacted]

The following comparator will be used in the Tolerance Phase of this investigation:

- Comparator A: non-sensate water-based lubricant
- Comparator B: non-sensate silicone-based lubricant

The composition of the IPs and comparator are presented in Table 5-1.

Table 5-1 Investigational Product – Quantitative Composition of Each Component per variant

[redacted]

[redacted] the lubricants will be assembled to GMP standards by the IMSU and certified by Reckitt Research and Development (R&D) Quality. The IPs will be shipped directly from IMSU to the clinical site.

5.2 Non-Investigational Products

Not applicable, as non-investigational product(s) is not to be supplied as part of this investigation.

5.3 Concomitant Therapies

This section is applicable to both subjects and male partners.

Any treatment considered necessary for the subject's/male partner's welfare may be administered and/or continued under the supervision of the investigator. Concomitant therapy, including prescription and non-prescription over-the-counter drugs, including vitamins, herbal and dietary supplements medication and non-pharmacological treatments such as physiotherapy, will be captured in the concomitant therapies page of the eCRF from the date of informed consent. Any changes in concomitant therapy during the investigation will be documented, including cessation of therapy, initiation of therapy and dose changes. The investigator will record the AE for which the concomitant therapy was administered in the eCRF.

Female subjects are permitted to continue any prescribed oral contraception, contraceptive devices and HRT if this is ongoing at the time of screening and recorded on the concomitant therapy eCRF form.

5.4 Packaging and Labelling and Supply / Resupply

A sufficient amount of IP and comparator to dispense to enrolled subjects will be packed and labelled along with spares in case of any issues / error during the investigation. The IPs and comparators will be labelled by the IMSU in accordance with EudraLex Volume 4 GMP Guidelines, Annex 13 - Manufacture of Investigational Medicinal Products, parts 26 to 33 (Labelling) and in accordance with directive 2003/94/EC as amended and including any other applicable national / state legislation or standards. The IPs and comparators will be assembled and shipped in bulk directly from the IMSU to the clinical site.

5.5 Storage Conditions

At the clinical site the Investigator must keep all IP supplies, including comparators, in a secure area with restricted access. The IPs and comparators should be stored at room temperature, dry place, and away from direct sunlight. The correct storage conditions will be monitored and recorded weekly. Any excursions from the correct conditions must immediately be reported to the Sponsor, where appropriate action will be agreed and documented.

5.6 Masking

This is an open label, parallel design clinical investigation and therefore is no intention to compare the IPs. For this purpose, the IPs and comparators will not be masked (i.e. the identity of the products will not be concealed).

To minimize the evaluation bias, oral tolerance assessments will be performed by the dermatologist who will remain blinded to the randomisation in the Tolerance Phase.

5.7 Emergency Unblinding Procedures

Not applicable, as per Section 5.6.

5.8 Accountability of Medical Device

The investigator will keep all the investigational supplies in a secure storage facility, accessible to those individuals authorised by the Investigator to dispense IPs and comparators. The Investigator or designated individual will maintain an inventory, which will include the description and quantity of each IP and comparator received during the investigation, as well as the record of materials that are dispensed and returned (i.e. how much, to whom and when). This inventory will be subject to review by the investigation monitor during monitoring visits.

5.9 Return and Destruction

The Investigator or designated individual will conduct a full IP and comparator supply reconciliation and will record the results of this reconciliation. Following review of this reconciliation documentation the clinical site will arrange for the return of all used and unused IPs and comparators to Reckitt IMSU to be destroyed at the end of the clinical investigation (upon finalisation of the Clinical Investigation Report (CIR). The IMSU reconciliation will be completed to confirm destruction.

6 INVESTIGATION PROCEDURES BY VARIABLE

6.1 Informed Consent

Due to the exposure of the male partner to the IPs, the inclusion of the subject into the investigation will require consent from both female and male partner (separately).

Prior to conducting any investigation-related activities, written informed consent must be obtained from the subject. No subject can enter the investigation before informed consent has been obtained. Upon signing the Informed Consent Form (ICF) the subject is enrolled into the investigation.

All subjects will be provided with oral and written information describing the nature and duration of the investigation and the procedures to be performed. Enough time needs to be given to the subject to decide whether to participate or not. The Investigator must explain to each subject the nature of the investigation, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. Each subject must be informed that participation in the investigation is voluntary and that she may withdraw from the investigation at any time and that withdrawal of consent will not affect her subsequent medical treatment or relationship with the treating physician. The subject must be informed that her medical records may be examined by authorised individuals other than their treating physician.

The subject should understand the information provided and the ICF before signing and dating the ICF. The Investigator or person obtaining consent must also sign and date the form. Each subject will be given a copy of the signed informed consent and written information.

The original signed ICF for each subject will be verified by the monitor and kept in the investigation centre investigational site files.

If new information should become available during the investigation of which subjects need to be aware, an updated ICF will be provided and the above process will be followed to confirm subjects

are happy to continue with the investigation. For subjects who have completed the investigation, the Investigator will decide if this new information needs to be provided to them.

6.2 Male Partners

Male partners of female subjects will be enrolled into the investigation and attend the clinical site for Visit 1 - Screening visit. Prior to conducting any investigation-related activities for the female subject, written informed consent will be obtained from the male partner. Each male partner will be provided with oral and written information describing the nature of the investigation, the IPs that his female partner will be testing and potential risks and benefits to them. Enough time needs to be given to the male partner to consider the participation. A female subject is free to participate in the investigation. However, if her male partner decides not to provide informed consent or withdraws from the investigation before completion, this means that the female subject will be withdrawn/can no longer participate. Each male partner must be informed that participation in the investigation is voluntary and that he may withdraw from the investigation at any time and that withdrawal of consent will not affect his subsequent medical treatment or relationship with the treating physician. The male partner must be informed that his medical records may be examined by authorised individuals other than their treating physician.

The original signed ICF for each male partner will be verified by the monitor and kept in the investigation centre investigational site files. If new information should become available during the investigation of which male partners need to be aware, an updated ICF will be provided and the above process will be followed to confirm male partners are happy to continue with the investigation. For female subjects who have completed the investigation, the Investigator will decide if this new information needs to be provided to male partners.

The eligibility of male partners will be assessed by the Investigator according to Section 4. Medical history and prior therapies (refer to Section 6.6), sex and age, lubricant use history will be collected

The CIP requires male partner to attend the clinical site for Visit 3 in the Treatment Phase and complete questionnaires as described in Section 7. During the investigation, if the male partner experiences any AE/ADE, the event must be collected. The reporting can be via a contact by the male partner with the clinical site or via the female subject at each visit or via the male partner at his visit. Instructions on how to report an AE/ADE and any changes in medication and consult with the clinical site for any safety concern will be described in the ICF.

6.3 Randomisation

This is an open label investigation and eligible subjects will be randomised to one of the two treatment groups by the use of a randomisation schedule generated in SAS version 9.4 and provided by the clinical research organisation (CRO).

Eligible subjects will be randomised in a 1:1 ratio to one of the two treatment regimes using permuted blocks of fixed size of 4. The randomisation will be stratified by menopausal status, namely pre-menopausal for Strata 1 or post-menopausal for Strata 2. There will be no more than 60% of subjects allocated from one strata.

22 subjects will be selected in a 1:1 treatment allocation ratio to participate in the Tolerance Phase of the investigation. To ensure that an approximately even distribution of pre- and post-menopausal women participate in the Tolerance Phase (up to a maximum of 60% from any one strata), subjects will be enrolled into the Tolerance Phase in sequential order as they are randomised into the main study until a maximum of 13 subjects are chosen from one strata. As soon as the first 13 subjects from one strata are enrolled into the Tolerance Phase, the remaining subjects will be chosen sequentially from the other strata. Enrolling subjects into the Tolerance Phase in sequential order will ensure an approximately even distribution from both treatment groups.

The randomisation schedule will also allocate which side of the mouth (left or right) the subjects will apply the test IP or the respective comparator, for the oral tolerance assessment in the tolerance phase. Assignment will be such that each test and comparator are assigned equally to the left and right side. The application always starts on the left-hand side.

In the oral assessment, IP A is always tested against Comparator A and IP B is always tested against Comparator B.

6.4 Administration of Medical Device

6.4.1 Tolerance Phase

6.4.1.1 Vulvovaginal Tolerance Phase

Subjects will be trained by the clinical site staff on the amount and how to apply their allocated IP to the vagina and intimate area. A single application, approximate 3 g amount of the IP, will be dispensed from the product container and applied to the vagina and vaginal area with fingers as per instructions for use and as per training given at the clinical site.

6.4.1.2 Oral Mucosal Tolerance Phase

Each subject will test one IP and one comparator according to the randomisation schedule. A pea-sized application of the allocated IP will be applied to the inner linings of the upper and lower lips of the subjects on one side of the mouth by the clinical site staff. A pea-sized application of the respective comparator will be applied to the other side of the mouth, again on the inner linings of the upper and lower lips of the subjects by the clinical site staff. The location of application (left or right side of the mouth) of the IP and its respective comparator will be determined according to the randomisation schedule. The application always starts on the left-hand side.

Oral tolerance assessments must be performed by the same trained dermatologist who will remain blinded to the randomisation in the Tolerance Phase.

6.4.2 Treatment Phase

Subjects will engage in vaginal penetrative sex at least once per week but will not be prohibited from engaging in other forms of sexual activity (e.g. receptive oral/anal sex, non-penetrative and penetrative masturbation with a sex toy, partner's fingers or solo). Subjects will not be prohibited from using condoms, but this will not be the only form of contraception and the use will be captured

in the diary. At product dispensing, subjects will be provided with a demonstration of a 3 g amount of lubricant for reference. The subjects will be asked to apply their allocated IP to the vagina and intimate area in approximately 3 g increments. The number of re-applications required during sexual intercourse will be recorded in the diary. Subjects can apply the IP up to 4 times per day where 3 g is considered to be a single application. Subjects will be expected to use their applicated IP at least once a week over a 4-week period. The number of penetrative penile/vaginal sexual intercourses may comprise twice in one week to account for a menstrual period break.

Regular lubricant users will be instructed to use the lubricant as they would normally i.e. for vaginal, anal and / or oral sexual intercourse, ensuring that the IP is used at least once a week for vaginal penetrative sexual intercourse. Those subjects who do not usually engage in anal or oral will be instructed to use the product for vaginal sex only, for safety purposes. Only the lubricant (IP) dispensed by the clinical site is permitted for use during the investigation. Subjects will be instructed to not use any other vaginal products, remedy, vaginal moisturiser. The weight of the IP will be recorded when dispensed and again when subjects return to the clinical site following the 4-week use period.

Subjects that use the IP less than once a week during penetrative penile/vaginal sexual intercourse and/or do not follow the study restrictions e.g. use of other vaginal product other than the dispensed IP are forms of non-compliance, in which case subjects will be reminded of the need to remain compliant and what this may mean to their participation in the investigation.

6.5 Demographics

Baseline characteristics and demographic information will be recorded. This will include:

1. For female subjects and their male partners:
   - Sex
   - Age
2. For female subjects only:
   - Menopausal status
   - Ethnicity
   - Date of last menstruation period
   - Height (in metres to the nearest cm)
   - Weight (kg to the nearest 0.1 kg; in indoor clothing and without shoes).

   Body Mass Index (BMI) will be calculated as follows: Body weight (kg) / [Height (m)]^2

6.6 Medical History and Prior Therapies

This section is applicable to both subjects and male partners.

Details of all relevant current and historical medical diseases, conditions or surgeries, i.e. gynecologically and orientated including ovariectomy, hysterectomy, cancer and dental/oral health oriented including dental/oral procedures, and the duration, will be recorded. All prior therapies

such as prescription or non-prescription drugs, including vitamins, herbal and dietary supplements and non-pharmacological treatments such as physiotherapy will also be recorded. Medical history for all prior therapies should be recorded. In addition, risk of STI, pregnancy and method of contraception to be used during the investigation will also be recorded.

6.7 Physical Examination

A complete physical examination of the subject will be performed by the Investigator or a medically qualified delegate (e.g. Principal Investigator / Co-Investigator) at Visit 1 – Screening Visit. A completed physical examination or selected examinations are to be performed if deemed necessary in the opinion of the Investigator in subsequent visits.

The examination will include at least general appearance, skin/subcutaneous tissue, ears/eyes/nose/mouth/throat, head/neck, respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological and lymph nodes (via visual inspection and palpation). Other body systems can be examined if required, at the discretion of the Investigator or delegate.

Subjects will also undergo a gynaecological examination by the gynaecologist (for both Tolerance Phase and Treatment Phase) and an oral examination by the dermatologist (for Tolerance Phase only). The gynaecological examination will include the pelvic examination, performed by the gynaecologist and any test per local practice to confirm the absence of infection, skin abnormalities and other health issues that would exclude the subject. The gynaecological examination will also involve checking for cutaneous irritancy (erythema, oedema, vulvar/vaginal dryness, leucorrhoea) and using a 5-point scale (1 = none; 2 = slight; 3 = minimal; 4 = moderate; 5 = severe) conducted in accordance with the principles described in assessing vaginal irritation in research (Mauck et al., 2000). The oral examination (for Tolerance Phase only) will involve checking the oral cavity for signs and symptoms of irritation including erythema, erosions on lips or oral mucosa, oedema and any other signs of clinical irritancy or conditions of the oral cavity as recognisable by the dermatologist.

6.8 Pregnancy Test

Urinary samples for pregnancy testing (for subjects of childbearing potential only) will be collected and prepared according to the Standard Operating Procedures (SOPs) of the clinical site conducting the analysis.

6.9 Verbal Rating Scale (VRS) of Dyspareunia and Vaginal Dryness

Subjects reporting regular discomfort during sexual intercourse when not using lubricant, will be asked to verbally rate the intensity of their dyspareunia (painful intercourse) and vaginal dryness in the previous three months prior to the screening visit using the 4-point VRS of Dyspareunia and Vaginal dryness. Subjects will be asked to rate the two symptoms using the following scale:

Dyspareunia 0-3 intensity scale:

- No pain [Absent (0)]
- Mild pain [Mild (1)]

- Moderate pain [Moderate (2)]
- Severe pain [Severe (3)]

Vaginal Dryness 0-3 intensity scale:

- No dryness [Absent (0)]
- Mild dryness [Mild (1)]
- Moderate dryness [Moderate (2)]
- Severe dryness [Severe (3)]

Those subjects that rate the intensity of their dyspareunia and vaginal dryness or just vaginal dryness a score of 1 (mild) or 2 (moderate) would meet the inclusion criterion.

6.10 Lubricant Use History

Subjects and male partners will be asked about their experience in using a lubricant(s), information such as (but not limited to) will be captured; user or non-user of lubricant, when does the subject use lubricant (i.e. for oral, anal, vaginal sexual intercourse), frequency of lubricant use.

6.11 Tolerance Phase Variables

6.11.1 Vaginal Epithelial Tolerability (VET) Assessment

Vaginal tolerability of the IP will be evaluated by the gynaecologist at baseline, 2 hours and 24 hours post single application. The gynaecologist will examine the vaginal dermal tissue for signs and symptoms of erythema, oedema, vulvar membrane dryness, leucorrhoea and other each sign and symptom will be scored using the following 5-point scale (in accordance with the principles described in assessing vaginal irritation in research (DeRogatis et al., 2014)):

- 1 = None
- 2 = Slight
- 3 = Minimal
- 4 = Moderate
- 5 = Severe

6.11.2 Global Assessment of Vulvovaginal Tolerance

At the end of the Tolerance Phase (or withdrawal if earlier) the gynaecologist will make a ‘global assessment’ of vulvovaginal tolerance for each subject for each IP based on measured parameters, any clinical signs of irritancy observed, subject’s perception of vulvovaginal tolerance (SPQ – Tolerance); taking into account the expected degree of irritancy for this type of product, using the following 5-point scale:

- 1 = Very Good
- 2 = Good
- 3 = Acceptable
- 4 = Poor

- 5 = Very Poor

6.11.3 Overall Vulvovaginal Tolerance Rating Statement

At the end of the Tolerance Phase, the gynaecologist will make an overall summary assessment of vulvovaginal tolerance of the IP, driven by Global Assessment of Vulvovaginal Tolerance and taking into consideration all tolerance assessments across all subjects and the nature of the product in its intended use, in the following format:

The product is very well / well / moderately well / not well / not at all well tolerated by all / most / some / a few subjects.

6.11.4 Oral Mucosal Tolerance

Oral mucosal tolerability of the IPs and comparator will be evaluated by the dermatologist via a lip test at baseline, 30 minutes, 2 hours and 24 hours post single application to the upper and lower inner lip. The dermatologist will examine the oral mucosa for signs and symptoms of erythema, erosions on lips or oral mucosa, oedema and any other signs of clinical irritancy as recognisable by the expert. Signs/symptoms will be scored using the following scale:

- 1= none
- 2 = slight
- 3 = minimal
- 4 = moderate
- 5 = severe

The presence of any adverse reactions (e.g., difficulty in breathing, oedema elsewhere on face, and anaphylaxis) will be recorded.

6.11.5 Global Assessment of Oral Mucosal Tolerance

At the end of the Tolerance Phase (or withdrawal if earlier) the dermatologist will make a 'global assessment' of oral mucosal tolerance of each IP and comparator based on measured parameters, any clinical signs of irritancy observed, subject's perception of oral mucosal tolerance (SPQ – Tolerance); taking into account the expected degree of irritancy for this type of product, using the following 5-point scale:

- 1 = Very Good
- 2 = Good
- 3 = Acceptable
- 4 = Poor
- 5 = Very Poor

6.11.6 Overall Oral Mucosal Tolerance Rating Statement

At the end of the Tolerance Phase, the dermatologist will make an overall summary assessment of tolerance of each IP and comparator driven by Global Assessment of Oral Mucosal Tolerance and

taking into consideration all oral mucosal tolerance assessments across all subjects and the nature of the product in its use for oral sex, in the following format:

The product is very well / well / moderately well / not well / not at all well tolerated by all / most / some / a few subjects.

[redacted]

6.11.9 Subject Perceived Questionnaire (SPQ) – Tolerance Phase

As part of the Tolerance Phase, subjects will be asked about their perception of tolerance post application. The subjects' perception of vulvovaginal tolerance and oral mucosal tolerance will be determined at 24 hours post application through a 5-point agreement scale (Likert scale) listed as:

- Strongly Agree
- Agree
- Neither Agree nor Disagree
- Disagree
- Strongly Disagree

In addition, the subject' perception of intensity of the sensation provided by the IP on vulvovaginal tolerance and oral mucosal tissue will be determined at 24 hours post application. This will be rated by subjects on an 11-point numeric rating scale (NRS), where 0 = "There is no sensation from the lubricant"; 5 = "The intensity of the sensation provided by the lubricant is just right"; 10 = "The intensity of the sensation provided by the lubricant is unbearable".

6.12 Treatment Phase Variables

6.12.1 Female Sexual Function Index (FSFI)

The FSFI is a 19-item self-report questionnaire (paper) to measure sexual functioning in women. The questionnaire assesses six domains of sexual function (sexual desire, sexual arousal, lubrication, orgasm, satisfaction and pain) as well as a total score. The questionnaire requires a 4-week recall.

6.12.2 Subject Diary

Subjects will be required to complete a paper diary for the run-in phase and a paper diary for the 4-week IP use period to capture the information (but not limited to):

- Date and time of IP use
- Number of vaginal penetrative sex occasions
- Site of IP application (for each sex occasion)
- Number of IP applications per sex occasion
- Details of additional sexual activity outside of vaginal penetrative sex
- Condom use
- Comments on experience with the IP during initial entry versus deeper penetration/thrusting
- Any changes in medication
- Any AEs
- Any other comments

6.12.3 Subject Perceived Questionnaire (SPQ) – Treatment Phase

During the Treatment Phase, subjects and male partners will be asked about their perception of the allocated IP, after first IP use (within 24 hours of intercourse) and after 4 weeks of IP use. Their perception will follow the 5-point agreement scale (Likert scale) listed as:

- Strongly Agree
- Agree
- Neither Agree nor Disagree
- Disagree
- Strongly Disagree

6.12.4 Global Evaluation of Product Effectiveness, Tolerability and Usability

At the end of the Treatment Phase (or withdrawal if earlier) subjects will be asked to provide their global evaluation of their allocated IP after using their allocated IP for 4-week. Subjects will be asked to rate their agreement using the following scale:

- Very Satisfied
- Somewhat Satisfied
- Neither Satisfied nor Dissatisfied

- Somewhat Dissatisfied
- Very Dissatisfied

6.12.5 Patients Global Impression of Change (PGIC)

At the end of the Treatment Phase (or withdrawal if earlier) subjects and male partners will be asked to complete a PGIC (Hugh H and Jennifer B, 2004). PGIC is a patient reported scale to assess patient perception of change in a condition or symptom following treatment. The subjects and male partners will be asked to rate the change in sexual intimacy experienced within their couple after using their allocated IP for 4-week. PGIC will be presented in a form of the visual analogue scale (VAS):

- -3 (Much Worse)
- -2
- -1
- 0 (No Change)
- 1
- 2
- 3 (Much Better)

[redacted]

6.13 Adverse Events

During scheduled visits, non-leading questions ('Are you experiencing any symptoms or complaints? / Have you felt unwell, suffered any complaints or taken any medication since… / Have you had any symptoms of complaints since the last time you were asked?') will be used to collect any AE/ADE experienced by the subject/male partner. Additionally, spontaneously reported AEs/ADEs will be collected. AE/ADE of male partners can be reported via a contact by the male partner with the clinical site or via the female subject at each visit or via the male partner at his visit.

The observation period for an individual subject/male partner will start after giving informed consent and will finish at the last visit of the Treatment Phase for the given individual subject/male partner. All AEs/ADEs that arise during the observation period will be recorded and an assessment of the AEs/ADEs will be performed as per Section 8.1 by a medically qualified Investigator. If a subject/male partner has an AE/ADE that is still ongoing at the last visit, an attempt will be made by the Investigator to follow this up as per Section 8.3.

If an untoward medical occurrence happens after the subject/male partner has signed the consent form but before administration of the device, it should be reported as an AE, including those associated with investigation procedures.

7 INVESTIGATION PROCEDURES BY VISIT

7.1 Investigation Flow Chart / Table of Investigation Procedures and Assessments

Table 7-1 Schedule of Assessments – Tolerance Phase

Procedure \ Period	Screening	Tolerance Phase						Treatment Phase		
	Visit 1	7-Day Wash-Out Period	Visit 2[1]			Visit 3[2]		Run-In Phase	Visit 2[3]	Visit 3[4]
			Baseline	30 mins	2 hrs	24 hrs				
Informed consent (including male partners)	X									
Inclusion / Exclusion (including male partners)	X		X[5]			X[5]			X[5]	X[5]
Verbal Rating Scale (VRS) of Dyspareunia and Vaginal Dryness[6]	X									
Demographics (including male partners)	X									
Medical history & prior therapies (including male partners)	X									
Concomitant medication (including male partners)	X	X	X	X	X	X		X	X	X
Physical examination	X		X[7]			X[7]			X[7]	X[7]
Pregnancy test	X					X[8]				X[8]
Lubricant Use History	X									

Procedure \ Period	Screening	Tolerance Phase					Treatment Phase		
	Visit 1	7-Day Wash-Out Period	Visit 2[1]			Visit 3[2]	Run-In Phase	Visit 2[3]	Visit 3[4]
			Baseline	30 mins	2 hrs	24 hrs			
Randomisation[9]	X								
Vaginal Epithelial Tolerability Assessment			X		X	X			
Global Assessment of Vulvovaginal Tolerance						X			
Overall Vulvovaginal Tolerance Rating Statement						X			
Oral Examination/Assessment			X	X	X	X			
Global Assessment of Oral Tolerance						X			
Overall Oral Tolerance Rating Statement						X			
SPQ – Tolerance Phase						X			
[redacted]			[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
[redacted]			[redacted]		[redacted]	[redacted]			
FSFI Questionnaire								X	X
SPQ – Treatment Phase (including male partners)								X[11]	X

Procedure \ Period	Screening	Tolerance Phase						Treatment Phase		
	Visit 1	7-Day Wash-Out Period	Visit 2[1]			Visit 3[2]	Run-In Phase	Visit 2[3]	Visit 3[4]
			Baseline	30 mins	2 hrs	24 hrs			
Global Evaluation of Product Effectiveness, Tolerability and Usability									X
Patients Global Impression of Change (PGIC) (including male partners)									X
Issue Subject Diary[12]	X					X		X	
Collect and Review Subject Diary								X	X
IP Weighed[13]								X	X
IP Dispense								X	
Collect Returned IP									X
Adverse Events (including male partners)	X	X	X	X	X	X	X	X	X

1. Tolerance Phase Visit 2 should be conducted within 10 days after Visit 1. Assessment window: 30 minutes ±15 minutes post application (oral mucosal tolerance only) and 2 hours ±15 minutes post application (VET, oral mucosal tolerance, [redacted]
2. Assessment window: 24 hours ±2 hours post application.
3. Visit 4 for subjects undergone the Tolerance Phase. Treatment Phase Visit 2 should be conducted within ±3 days after the completion of the 4-week Run-In Phase.
4. Visit 5 for subjects undergone the Tolerance Phase. Treatment Phase Visit 3 should be conducted within ±3 days after the completion of the 4-week IP use period.
5. Eligibility to be confirmed following screening assessments. Continued edibility will be confirmed at each clinical site visit.
6. Subjects having a score of 1 or 2 for vaginal dryness and 1 or 2 for dyspareunia on the VRS are to be considered for inclusion into the investigation.

7. Physical examination, including gynaecological examination (Tolerance and Treatment phase) and oral examination (Tolerance Phase only), are to be performed if deemed necessary in the opinion of the Investigator.
8. Pregnancy test if deemed necessary by the Investigator.
9. Subjects will be randomised into the investigation upon completion of the screening activities and confirmation of subject's eligibility.
10. [redacted]
11. An SPQ is to be completed within 24 hours after first use of the allocated IP.
12. In the Treatment Phase, the diary will be issued at Visit 1 to capture subjects' compliance such as IP use, number of sexual acts etc during the run-in phase. A second diary will be issued at Visit 2 to capture their compliance over the 4-week IP use period.
13. In the Treatment Phase, IP will be weighed prior to being dispensed at Visit 2 and weighed upon being returned by subjects at Visit 3.

7.2 Visit 1 – Screening Visit

At the screening visit, subjects and male partners will be informed about the investigation as described in Section 6.1 and Section 6.2. They will be asked to provide written informed consent for their participation in the investigation, prior to performing any investigation specific assessments. Once informed consent has been obtained, the subjects will undergo clinical assessments consisting of:

- Demographics (including male partners)
- Medical history and prior therapies (including male partners)
- Physical examination, including gynaecological examination and oral examination
- The last menstrual period (the first date and the last date)
- Pregnancy test (for subjects of childbearing potential only)
- Concomitant medication and AEs (including male partners)
- Completion of VRS of dyspareunia and vaginal dryness
- Lubricant use history

Once screening activities have been completed and results are available confirming the subject's suitability to enter the investigation as per the inclusion/exclusion criteria, subjects and male partners will be reminded of the investigation's restrictions as per Section 4.4. Subjects will be randomised into one of two treatment groups using [redacted]. Each group will include an approximate 1:1 ratio of pre-menopausal to post-menopausal females, with an allowed difference of up to 40:60 (up to a maximum of 60% in either sub-population).

A subset of 22 subjects will undergo the Tolerance Phase of the investigation prior to entering the Treatment Phase per the randomisation schedule. Subjects entering the Treatment Phase directly will be issued a diary and instructed to complete during the run-in phase.

All assessments conducted during the screening visit are detailed in Section 6 and summarised in Table 7-1. All clinical assessments and test results will be entered into each subject's eCRF.

7.3 Tolerance Phase

7.3.1 Wash-Out Period

Subjects participating in the Tolerance Phase, will undergo a 7-day wash-out period. During this period, subjects are not permitted to use any personal lubricants or other remedies for vaginal dryness and will be asked to refrain from engaging in vaginal sex or any other vaginal penetrative sexual activity e.g. digital stimulation or use of sex toys. Subjects will also be prohibited from using any new oral products that are irregular to their normal dental hygiene routine or eating any new foods outside their normal diet.

7.3.2 Visit 2

Visit 2 should be conducted within 10 days after Visit 1. All requirements in the wash-out period must be followed until subjects attend the clinical site for Visit 2.

Following a 7-day wash-out period, subjects will return to the clinical site for the Tolerance Phase, where subjects' continued eligibility will be confirmed. Physical examination will be carried out if necessary, in the opinion of the investigator.

Once on the clinical site, subjects will be provided with a snack and drink, ahead of an oral water rinse. After the oral water rinse subjects will participate in an additional 30-minute oral wash out period during which they will be asked to refrain from using any oral products or consuming any foods/drinks. If necessary, subjects may have water, and this will be recorded.

The following baseline assessments and measurement will be performed prior to IP application:

- Vaginal Epithelial Tolerability (VET), performed by the gynaecologist
- Oral examination by the dermatologist after additional 30-minute wash-out
- [redacted]
- [redacted]
- [redacted]

For the vulvovaginal assessments, subjects will be trained by the site staff on how to apply the IP to the vagina and intimate area and will then make the single application of lubricant at the clinical site in preparation for the 2-hour post application vulvovaginal assessment. For the oral assessments, the clinical site staff will apply a pea-sized application of the IP and the respective comparator to the inner linings of the upper and lower lips of the subject on both sides of the mouth, according to the randomisation schedule. Subjects will be assessed at 30 minutes (±15 minutes) post application (oral mucosal tolerance only) and 2 hours (±15 minutes) post application (VET, oral mucosal tolerance, [redacted] In the first 2 hours post application, subjects will be asked to refrain from consuming any foods/drinks. If necessary, subjects may have water, and this will be recorded.

Subject's last menstrual period (the first date and the last date) will be recorded if the data is different from Visit 1. AEs will be collected using a general non-leading question. In addition, spontaneously reported AEs will be collected. Concomitant medication changes will be recorded.

While subjects are at home, they will be instructed to abstain from any vaginal penetrative activity including sexual activity or insertion of tampons and will refrain from using any vaginal products such as moisturisers or intimate washes. They will also be instructed to eat and drink as normal however again will be prohibited from using any new oral products that are irregular to their normal dental hygiene routine or eating any new foods outside their normal diet. Subjects will not be provided with any product to take home as there will be no additional applications during the Tolerance Phase.

All assessments conducted during the Visit 2 are detailed in Section 6 and summarised in Table 7-1. All clinical assessments and test results will be entered into each subject's eCRF.

7.3.3 Visit 3

Subjects will return to the clinical site for their 24-hour assessment. After confirmation of continued eligibility, subjects will undergo the following clinical assessments within the window of 24 hours ±2 hours:

- Vaginal Epithelial Tolerability (VET), performed by the gynaecologist
- Oral Assessment by the dermatologist
- [redacted]

[redacted]

Subjects will be asked to complete the SPQ – Tolerance Phase at the clinical site. At the end of the Tolerance Phase, the gynaecologist will complete a Global Assessment of Vulvovaginal/Oral Mucosal Tolerance for each subject and provide an Overall Vulvovaginal/Oral Mucosal Tolerance Rating Statement for each IP. The Investigator (in consultation with the gynaecologist and the dermatologist) will determine if the subject remains eligible to enter the Treatment Phase of the investigation, as per the inclusion/exclusion criteria and given that the subject has not experienced any untoward medical occurrence. Additionally, subjects will be issued a diary and instructed to complete during the run-in phase as they enter the Treatment Phase.

Subject's last menstrual period (the first date and the last date) will be recorded if the data is different from Visit 2. AEs will be collected using a general non-leading question. In addition, spontaneously reported AEs will be collected. Concomitant medication changes will be recorded.

All assessments conducted during the Visit 3 are detailed in Section 6 and summarised in Table 7-1. All clinical assessments and test results will be entered into each subject's eCRF.

7.4 Treatment Phase

7.4.1 Run-In Phase

Following the confirmation of subject's eligibility, subjects entering the Treatment Phase will undergo a 4-week run-in phase. Those subjects that have completed the Tolerance Phase of the investigation, will move into the 4-week run-in phase of the Treatment Phase. During this run-in phase, subjects will be asked to refrain from using any personal lubricants or remedies for vaginal dryness during sexual activity. Subjects will be asked to consent to engaging in vaginal penetrative sex at least once per week during this 4-week period. The number of sexual intercourses may comprise twice in one week to account for a menstrual period break. Subjects will be asked to record into their diary the number and frequency of coital acts during this period, including when subjects were unable to have sexual intercourse without the use of a lubricant and/or for menstrual bleeding (pre-menopausal women).

7.4.2 Visit 2 – Baseline

This is Visit 4 for subjects undergone the Tolerance Phase. This visit should be conducted within ±3 days after the completion of the 4-week Run-In Phase.

Subjects will return to the clinical site following the run-in phase, where the following will be performed:

- Assess subject's continued eligibility as per inclusion/exclusion criteria
- Physical examination, including gynaecological examination (if necessary, in the opinion of the Investigator)
- Completion of FSFI by the subject
- [redacted]
- [redacted]
- Collection of diary and review for compliance
- Issuing new diary for the IP use period & SPQ – Treatment Phase
- Weigh and dispense IP
- Recording of AEs and concomitant medication changes
- Recording subject's last menstrual period (the first date and the last date)

Upon completion of the FSFI, subjects will be trained on how to apply the IP to the vagina. Subject's allocated IP (as per the randomisation schedule) will be weighed prior to being dispensed for the subject to use at home for a 4-week IP use period. Subjects will be instructed to use their allocated IP when engaging in vaginal penetrative intercourse at least once a week. Regular lubricant users will be instructed to use the lubricant as they usually would i.e. for vaginal, anal and/or oral sexual intercourse, ensuring that the IP is used at least once a week for penile/vaginal intercourse. For safety purposes, those subjects who do not usually engage in anal or oral will be instructed to use the IP for penile/vaginal sexual intercourse only.

Subjects will also be issued a diary to record number of sex occasions, site of lubricant application and number of lubricant applications per sex occasion. Additionally, subjects will be instructed that the subject and the male partner should complete an SPQ – Treatment Phase after the first use of the IP at home, within 24 hours of the intercourse. Subjects will be reminded of the study restrictions as per Section 4.4, after which subjects will be permitted to leave the clinical site.

All assessments conducted during Visit 2 are detailed in Section 6 and summarised in Table 7-1. All clinical assessments and test results will be entered into each subject's eCRF.

7.4.3 Visit 3 (End of Investigation)

This is Visit 5 for subjects who have participated in the Tolerance Phase. This visit should be conducted within ±3 days after the completion of the 4-week IP use period.

Subjects and male partners will return to the clinical site after the 4-week IP use period, where there following assessments will be performed:

- Completion of FSFI by the subject
- Completion of an SPQ – Treatment Phase by the subject and the male partner
- Completion of Global Evaluation of Product Effectiveness, Tolerability and Usability by the subject
- Completion of PGIC by the subject and the male partner

- Physical examination, including gynaecological examination (if necessary, in the opinion of the Investigator)
- Collection of diary and review for compliance
- Collect and weigh returned IP
- [redacted]
- [redacted]
- Recording of AEs and concomitant medication changes (including the male partner)
- Recording subject's last menstrual period (the first date and the last date)

All assessments conducted during the Visit 3 are detailed in Section 6 and summarised in Table 7-1. All clinical assessments and test results will be entered into each subject's eCRF.

7.5 Unscheduled Visits

If unscheduled visits occur, the Investigator must record the reason for unscheduled visit, including any AEs/ADEs that the subject or the male partner has experienced since their last visit, concomitant medication changes, withdrawal (if deemed appropriate) and any clinical assessments deemed appropriate for their clinical care.

Unscheduled visits should not alter the timing of the routine investigation schedule.

8 SAFETY REPORTING

In this investigation, safety reporting is applicable for both female subjects and male partners by following the process described in this section, which the term of 'subject' refers to both female and male partners.

Safety Reporting in the investigation are in compliance with the Regulation (EU) 2017/745, the guidance of MDCG 2020-10/1 and the guidelines on medical devices, MEDDEV 2.7/3 revision 3, May 2015.

8.1 Adverse Event Definitions

Adverse Event

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device.

This definition includes events that are anticipated as well as unanticipated events.

This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

Adverse Device Effect

An Adverse Device Effect (ADE) is an AE related to the use of an investigational medical device.

This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the

investigational medical device. This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device. This includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device. This includes any event that is a result of a use error or intentional misuse.

Device Deficiency

Any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, misuse or use errors or inadequacy in information supplied by the manufacturer.

Serious Adverse Event

A Serious Adverse Event (SAE) is any AE that led to any of the following:

a. death,
b. serious deterioration in health of the subject, that resulted in any of the following:
    - life-threatening illness or injury,
    - permanent impairment of a body structure or a body function,
    - hospitalisation or prolongation of patient hospitalisation,
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
    - chronic disease,
c. foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

A planned hospitalisation for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be an SAE.

This includes device deficiencies that might have led to a SAE if

a. suitable action had not been taken or
b. intervention had not been made or
c. if circumstances had been less fortunate.

Serious Adverse Device Effect

A Serious Adverse Device Effect (SADE) is an ADE that has resulted in any of the consequences characteristic of a SAE.

Unanticipated Serious Adverse Device Effect

An Unanticipated Serious Adverse Device Effect (USADE) is an effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Anticipated Serious Adverse Device Effect

Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the current version of risk analysis report.

8.2 Assessment of Adverse Events

All AEs that arise after the subject has given informed consent will be recorded in the subject's source documents and eCRF. AEs can be reported spontaneously by the subject or in response to non-leading questioning, observation by the Investigator or be a significant laboratory abnormality.

All AEs, ADEs, SAEs, SADEs and USADEs are collected, fully investigated and documented.

SAE / SADE / USADEs should be followed until resolution or stabilisation. Subjects with ongoing SAE / SADE / USADEs at investigation termination will be further followed up until recovery or until stabilisation of the disease after termination.

For each SAE, a causality assessment of the event to the investigational device, the comparator or the investigation procedure must be performed. For each AE, the relationship between the use of the investigational device (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized. The relationship must be determined by the Investigator (if medically qualified) or by a medically qualified Co-Investigator.

Relationship	Description
Not related	Relationship to the investigational device, comparator or procedures can be excluded when: ▪ the event is not a known side effect of the product category the device belongs to or of similar devices and procedures. ▪ the event has no temporal relationship with the use of the investigational device or the procedures related to application of the investigational device. ▪ the serious adverse event does not follow a known response pattern to the investigational device (if the response pattern is previously known) and is biologically implausible. ▪ the discontinuation of investigational device application or the reduction of the level of activation / exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation / exposure), do not impact on the serious adverse event. ▪ the event involves a body-site or an organ that cannot be affected by the device or procedure. ▪ the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness / clinical condition, an effect of another device, drug, treatment or other risk factors). ▪ the event does not depend on a false result given by the investigational device used for diagnosis, when applicable. In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device / procedures and the serious adverse event.
Possible	The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness / clinical condition or / and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and / or the event cannot reasonably explained by another cause.
Causal Relationship	The serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when: ▪ the event is a known side effect of the product category the device belongs to or of similar devices and procedures.

	▪ the event has a temporal relationship with investigational device use / application or procedures. ▪ the event involves a body-site or organ that: o the investigational device or procedures are applied to o the investigational device or procedures have an effect on ▪ the serious adverse event follows a known response pattern to the investigational device (if the response pattern is previously known). ▪ the discontinuation of investigational device application (or reduction of the level of activation / exposure) and reintroduction of its use (or increase of the level of activation / exposure), impact on the serious adverse event (when clinically feasible). ▪ other possible causes (e.g. an underlying or concurrent illness / clinical condition or / and an effect of another device, drug or treatment) have been adequately ruled out. ▪ harm to the subject is due to error in use. ▪ the event depends on a false result given by the investigational device used for diagnosis, when applicable. In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device / procedures and the serious adverse event.

For each AE a severity description should be given.

Severity	Description
Mild	The event is easily tolerated and does not limit everyday activities; the subject may experience slight discomfort.
Moderate	The event is sufficiently discomforting to interfere with everyday activities.
Severe	The event prevents normal everyday activities; the subject may experience intolerable discomfort or pain.

Expectedness for each AE will be determined based on the information in sections 3.4 and 4 of the Investigator's Brochure.

Coding of AEs and medical history will be done using Medical Dictionary for Regulatory Activities (MedDRA) 25.1, or the most recent version if this has changed. If there is an update to MedDRA during the course of the investigation the most recent version will be used by the CRO.

Concomitant medications are coded by the CRO using the WHO dictionary (including ATC coding).

8.3 Reporting of Adverse Events

In the event of an SAE, SADE, USADE or device deficiency that could have led to an SAE, the Investigator must report the event using the appropriate form to the Sponsor's Adverse Event Management Team (AEMT) by email: [redacted] including in the email vendor and Sponsor Study Managers within 24 hours of knowledge of the event.

The out of hours emergency phone number is [redacted] if consultation is required by the Investigator.

This emergency phone number will be confirmed to the Investigator at the Investigation Initiation Visit.

All SAE / SADE / USADE forms must be provided via email including reports of device deficiency that could have led to a SAE/ SADE/ USADE. Any inconsistencies in the information received from the Investigator will be clarified on an updated SAE / SADE form. The Investigator must retain a copy of all the forms in the Investigator Site File.

The Investigator, if required by regulations, must inform their local Independent Ethics Committee (IEC) / Research Ethics Committee (REC) / Institutional Review Board (IRB) of all SAE / SADE / USADEs and reportable Device Deficiencies occurring in the investigation as per Sponsor instructions as described in the Safety Management Plan.

SAE / SADE / USADEs, Device Deficiencies will be reported to the appropriate regulatory authorities by the Sponsor in accordance with the authorities' requirements. The Sponsor is responsible for expedited reporting of all SAE / SADE / USADEs and reportable Device Deficiencies to relevant authorities. The Investigator is responsible for expedited reporting of all SAE / SADE / USADEs and reportable device deficiencies to the IECs / IRBs as required by regulations. If the event requires expedited reporting, the AEMT and Investigator will take actions as per the investigation specific Safety Management Plan.

The Investigator must report all reportable events to the sponsor immediately but not later than 24 hours after investigational site investigation personnel's awareness of the event.

8.4 Follow-up of Adverse Events

All SAE / SADE / USADEs and all AE / ADEs that have not resolved by the end of the investigation will be followed up by the Investigator until resolution or until the Investigator believes there will be no further change, whichever is the earlier. This may involve the subject making additional visits to the site.

In the case of loss to follow-up, at least two documented attempts to contact the subject must be made by the Investigator or designee before this is defined.

The end of the investigation is defined as the last visit of the last subject in the investigation.

All SAE/SADE/USADEs and all AE/ADE that cause premature withdrawal of the subject from the investigation and have not resolved by the end of the clinical investigation will be followed up by the Investigator until resolution or until the Investigator believes there will be no further change.

This may involve the subject making additional visits to the site. The minimum data required are the subject number, suspected investigational product, final outcome and date, which may be obtained by the Investigator in a documented telephone conversation with the subject or subject's general practitioner (GP) / Primary Care Physician (PCP).

Subjects who experience the onset of an (S)AE after the last visit (end of the investigation) will not need to be recorded.

8.5 Misuse and Medical Device administration Errors

The Sponsor defines "misuse" as situations where the medical device is intentionally and inappropriately used not in accordance with the authorised product information.

All incidences of misuse are reportable to the Sponsor irrespective of the presence of an associated AE. The misuse and any associated untoward event will be captured on an AE / ADE eCRF page or on a SAE / SADE / USADE form.

Medical device administration errors are any unintentional errors in administration which relates to:

- Using / being administered an incorrect medical device
- Using / being administered the medical device by the wrong route of administration / application
- The accidental administration of the medical device to a person who is not a subject within the investigation

Medical device administration errors are reportable to the Sponsor irrespective of the presence of an associated AE. Medical device administration errors with or without an associated untoward event will be captured on an AE / ADE eCRF page or on a SAE / SADE / USADE form.

8.6 Pregnancy

Pregnancy in a female subject is considered a collectable event and will be recorded as an AE in all cases. It will be qualified as an SAE only if it fulfils SAE criteria.

Pregnant subjects must immediately be withdrawn from the clinical investigation and the Sponsor must be promptly notified of the event. Any pregnancy during the investigation will be reported to the Sponsor within 24 hours of becoming aware of the pregnancy. The course and outcome of the pregnancy should be followed up carefully by the Sponsor Pharmacovigilance personnel (Drug Safety Officer) as part of their safety monitoring responsibilities and will not form part of the investigation dataset. Any abnormal outcome regarding the mother or the child should be documented and reported.

9 STATISTICAL CONSIDERATIONS

All statistical analysis will be conducted by the Vendor. The statistical software that will be used for the analysis will be SAS® version 9.4 or newer. All data will be listed by treatment group.

In general, continuous data will be summarised by treatment group using the following descriptive statistics: n, mean, standard deviation, median, minimum and maximum. Categorical data will be summarised by treatment group as the number and percentage of subjects in each category.

9.1 Statistical Analysis Plan

Details of statistical methods and analysis will be documented in the Statistical Analysis Plan (SAP) which will be finalised before the first subject is screened.

If there are any deviations to the proposed statistical analysis as described in this protocol these will either be documented in a protocol amendment and/or the final SAP prior to First Subject First Visit with the rationale and impact of the changes addressed.

9.2 Interim Analysis

No interim analysis will be performed.

9.3 Analysis Datasets

The Full Analysis Set (FAS) will include all randomised subjects who enter the Treatment Phase of the study. The FAS will be used to assess the primary endpoint and all other endpoints that are assessed during the Treatment Phase, with the exception of adverse events. Subjects will be assigned to treatment to which they were randomised.

For the FSFI (total score and percentage of subjects achieving at least a 4-point change in total score), an analysis will also be performed on the Per Protocol (PP) population. The PP population will exclude subjects who have not been compliant with the requirements of at least one coital act per week during both the run-in and 4-week IP use period of the Treatment Phase, as well as using IP at least once per week for penile/vaginal intercourse during the treatment period. In addition, subjects who use less than 80% of their assigned product (<9.6g) will be removed from the PP population. Subjects may be excluded from the PP population due to other reasons that may impact the evaluation of study products and these will be identified prior to database lock. Subjects will be assigned to treatment received.

The Safety Population will include all randomised subjects and will include subjects who take part in the Tolerance Phase and/or the Treatment Phase. The Safety Population will be used for producing demographic, adverse event and other safety tables. Subjects will be assigned to treatment received.

9.4 Subject Disposition and Characteristics

Subject disposition and demographic characteristics will be presented by treatment group and overall. Frequencies and percentages will be used to present the number of subjects that

participated in each phase of the study (Tolerance Phase and Treatment Phase), the number that completed the study, number of subjects withdrawn as well as the reason of withdrawal if that is provided. Demographic characteristics of the subjects such as gender, race and menopausal status will be presented using frequencies and percentages. The age of the subjects, height, weight and BMI will be presented using summary statistics (mean, standard deviation (SD) median, minimum and maximum). Any other baseline characteristics will be presented using either frequencies and percentages or summary statistics, as appropriate.

9.5 Statistical Analyses

9.5.1 Primary Endpoint(s)

9.5.1.1 Primary Analysis

The primary endpoint for the clinical investigation is the change from baseline in Total FSFI score assessed at the end of the 4-week IP use period. An increase of at least 4 points in the FSFI score from baseline to 4-weeks post-lubricant use is considered a clinically important change. The change score will be calculated by subtracting the score at the end of the 4-week run-in period (baseline) from the score at the end of the 4-week IP use period. A positive change value indicates an improvement in sexual function.

The FSFI questionnaire (Appendix A) consists of 19 items across six domains. The answer choices in the FSFI carry a number of points and are summed to obtain six domain (subscale) scores and an overall score. The domain scores are obtained as the sum of points attributed to questions in that domain multiplied by the domain factor.

The following table describes the six domains, their corresponding items and possible range, as well as the domain factor.

Table 9-1 Female Sexual Function Index Domain Scores and Full-Scale Score

Domain	Items	Score range	Factor	Min score	Max score
Desire	1, 2	1 - 5	0.6	1.2	6
Arousal	3, 4, 5, 6	0 - 5	0.3	0	6
Lubrication	7, 8, 9, 10	0 - 5	0.3	0	6
Orgasm	11, 12, 13	0 - 5	0.4	0	6
Satisfaction	14, 15, 16	0/1 - 5	0.4	0.8	6
Pain	17, 18 19	0 - 5	0.4	0	6
Scale range				2	36

For the primary analysis, the Total FSFI Score at Visit 3 of the Treatment Phase is compared to its baseline value using a paired t-test. The statistical testing is carried out separately for each IP and consequently a single null and alternative hypothesis is defined for each IP. This results in two individual hypothesis pairs, which apply analogously to the following example for both IPs:

H_0: The Total FSFI score at Visit 3 of the Treatment Phase shows no difference from the corresponding baseline score.

H_1: The Total FSFI score at Visit 3 of the Treatment Phase shows a difference from the corresponding baseline score.

Theses hypotheses are expressed mathematically by

H_0: $\mu_{Baseline} = \mu_{V3}$

H_1: $\mu_{Baseline} \neq \mu_{V3}$

where $\mu_{Baseline}$ is the mean total FSFI Score at Baseline and μ_{V3} is the mean total FSFI Score at Visit 3 of the Treatment Phase.

Since the primary endpoint is being evaluated for each product separately, the resulting p-values will be compared to a critical alpha threshold that will be adjusted according to the Bonferroni-Holm method to ensure the Family Wise Error is controlled at 5%. For each treatment group, the Total FSFI will be summarised as actual scores at baseline and at 4 weeks, as well as change from baseline, using N, mean, standard deviation (SD), standard error (SE), median, minimum and maximum. The mean change from baseline in Total FSFI will also be presented with Bonferroni-corrected 97.5% confidence intervals (CI) to account for the 2 treatment comparisons. If the within-subject differences are not Normally distributed, a Wilcoxon signed rank test will be used to compare the change from baseline. In this case, Hodges-Lehmann 97.5% confidence intervals will be calculated.

Additionally, the number and percentage of subjects (including a 95% confidence interval calculated using the Wilson score method) achieving a 4-point improvement in Total FSFI at 4 weeks will be presented by treatment group. This will indicate the percentage of subjects who achieve the pre-defined MCID.

The handling of missing response on the FSFI is described in Section 9.8.

9.5.1.2 Secondary Analysis

The analyses described in Section 9.5.1.1 will be repeated for the PP population. In addition, for each treatment group, the Total FSFI will be summarised as actual scores at baseline and at 4 weeks, as well as change from baseline for the pre- and post-menopausal subgroups (using the FAS population). No hypothesis testing will be performed for the subgroup analyses.

9.5.2 Secondary Endpoints

9.5.2.1 Secondary Endpoint Analyses

For each of the secondary endpoints, hypothesis testing will not be performed, unless stated otherwise. Since the secondary endpoints are for supportive evidence only, no adjustments to p-values will be made.

The secondary endpoints are:

Treatment Phase:

- Number and percentage of subjects who achieve at least 4-point increase in total FSFI between baseline and 4 weeks.

For each treatment group and overall, the number and percentage of subjects who achieve an improvement of at least 4 points in the FSFI total score will be determined. The percentage and the 95% CI based on the Wilson Score method will be presented.

- Number and percentage of subjects who transition from sexual dysfunction (≤26.55 total FSFI score) to sexual function (>26.55 total FSFI score) between baseline and 4 weeks.

For each treatment group and overall, the number and percentage of subjects who transition from sexual dysfunction (≤26.55 total FSFI score) to sexual function (>26.55 total FSFI score) between baseline and 4 weeks will be determined. Also, the number of subjects categorised as sexual function at 4 weeks will be compared to the number categorised as sexual function at baseline, using McNemar's test. This comparison will be performed by treatment group and overall.

- Change from baseline in the FSFI individual domain scores (desire, arousal, lubrication, orgasm, satisfaction, and pain) at 4 weeks.

For each treatment group, the FSFI individual domain scores will be summarised as actual scores at baseline and at 4 weeks, as well as change from baseline, using n, mean, standard deviation (SD), median, minimum and maximum. Also, for each treatment group, the scores at 4 weeks will be compared to baseline using a paired t-test or Wilcoxon signed rank test, as appropriate.

For this secondary endpoint, the following pairs of hypotheses apply, formulated analogously for all domain scores:

H_0: The FSFI domain score at Visit 3 of the Treatment Phase shows no difference from the corresponding baseline score.

H_1: The FSFI domain score at Visit 3 of the Treatment Phase shows a difference from the corresponding baseline score.

Since testing is done within the non-confirmatory secondary endpoints, there is no adjustment for multiple testing.

- SPQs after first use at home and after 4 weeks

For each treatment group, for females and males separately, responses to the SPQ questions will be summarised at each time point (after first use at home and at the end of 4 weeks) as the number and percentage of subjects in each category (Strongly Agree, Agree, Neither Agree or disagree,

Disagree, Strongly Disagree), and also the number and percent in the top 2 categories (Strongly Agree, Agree) for each question.

- Subjects' Global Evaluation of product effectiveness, tolerability and device usability after 4 weeks

For each treatment group, the number and percentage of subjects answering in each category (Greatly Satisfied, Very Satisfied, Moderately Satisfied, Satisfied, Dissatisfied, Very Dissatisfied) will be presented.

- Patient Global Impression of Change at 4 weeks

For each treatment group, for females and males separately, the number and percentage in each of the PGIC categories (-3, -2, -1, 0, +1, +2, +3) at the end of 4 weeks will be summarised using a frequency table. In addition, the number and percentage of subjects who record an improvement of at least 2 points (including a 95% confidence interval calculated using the Wilson score method) will be presented.

Tolerance Phase:

Since only approximately 10 subjects from each treatment group will participate in the Tolerance Phase, all endpoints will be summarised using descriptive statistics only, with no hypothesis testing.

- Vaginal Epithelial Tolerability (none, slight, minimal, moderate, severe)

For each treatment group, the number and percentage of subjects assessed in each category (None, Slight, Minimal, Moderate, Severe) at each time point (baseline, 2 and 24 hours after single use) will be presented.

- Subject Perception of Vulvovaginal Tolerance of the two personal lubricants determined through Subject Perceived Questions at 24 hours post single application.

For each treatment group, the number and percentage of subjects in each category (Strongly Agree, Agree, Neither Agree or disagree, Disagree, Strongly Disagree), and also the number and percent in the top 2 categories (Strongly Agree, Agree) will be presented.

- Global Assessment of Vulvovaginal Tolerance for each subject at 24 hours post single application as determined by the gynaecologist.

At the end of the Tolerance Phase the gynaecologist will make a global assessment of vulvovaginal tolerance, and the number and percentage of subjects in each category (Very Good, Good, Acceptable, Poor, Very Poor) will be presented by treatment group.

- Overall Vulvovaginal Tolerance Rating Statement for each personal lubricant as determined by the gynaecologist.

At the end of the Tolerance Phase, the gynaecologist will make an overall summary assessment of vulvovaginal tolerance of the IP as very well / well / moderately well / not well / not at all well tolerated by all / most / some / a few subjects.

- An assessment of the oral mucosal tolerance of the personal lubricants at baseline, 30 minutes, 2 and 24 hours post single application to the upper and lower inner lip as assessed by dermatologist.

At each timepoint, the number and percentage of subjects in each category (None, Slight, Minimal, Moderate, Severe) will be presented for by treatment group and for each comparator group.

- Subject Perception of Oral Mucosal Tolerance of the two personal lubricants determined through Subject Perceived Questions at 24 hours post single application.

For each treatment group, the number and percentage of subjects in each category (Strongly Agree, Agree, Neither Agree or disagree, Disagree, Strongly Disagree), and also the number and percent in the top 2 categories (Strongly Agree, Agree) will be presented.

- Global Assessment of Oral Mucosal Tolerance for each subject at 24 hours post single application as determined by the dermatologist.

At the end of the Tolerance Phase the gynaecologist will make a global assessment of Oral Mucosal tolerance, and the number and percentage of subjects in each category (Very Good, Good, Acceptable, Poor, Very Poor) will be presented by treatment group.

- Overall Oral Mucosal Tolerance Rating Statement for each personal lubricant as determined by the dermatologist.

At the end of the Tolerance Phase, the gynaecologist will make an overall summary assessment of Oral Mucosal tolerance of each IP and comparator as very well / well / moderately well / not well / not at all well tolerated by all / most / some / a few subjects.

[redacted]

9.6 Description Statistics and Listings

Data related to the primary and secondary endpoints will be summarised using descriptive statistics where appropriate, and subject-level data will be provided in data listings.

Product usage will be summarised using descriptive statistics (total amount used and number of times product was used). Sexual activity will be summarised using descriptive statistics.

9.7 Adverse Events

AEs from both the Tolerance Phase and Treatment Phase will be summarised together. Safety endpoints will include incidence of treatment-emergent AEs (TE AEs), ADEs (TE ADEs) and concomitant medications.

The MedDRA (the most recent version) will be used to classify all AEs with respect to system organ class and preferred term. AE summaries will include only TE AEs and TE ADEs, which will be summarised (incidence and frequency) for each treatment group. In addition, TE AEs and TE ADEs will be summarised according to relationship to the device and study procedures. AEs for females and their male partners will be summarised separately.

Concomitant medication usage will be listed.

9.8 Handling of Missing Data and Drop-outs

All data will be analysed as collected; missing data due to premature discontinuation or any other reason will be left as missing. For the FSFI, in order to minimise the number of missing values for the FSFI subscale and Total scores, missing item responses will be handled as follows. A subscale score will be calculated as long as at least half of the items on the given subscale have valid, non-missing responses. Specifically, each subscale must have at least two non-missing responses, except for Desire, which has only two items and requires only one non-missing response. The Total FSFI score will be calculated as long as at least five out of the six subscale scores are present. Scores calculated in the presence of missing items will be pro-rated so that the theoretical minimum and maximum values are the same as those scores from complete data.

10 DATA HANDLING AND RECORD KEEPING

10.1 Case Report Forms

For each enrolled subject, an eCRF using fully validated software that conforms to 21 CFR Part 11 requirements, will be maintained. In the event of a screen failure, data will be recorded in the eCRF up until the point of screen failure. The Investigator is responsible for the quality of the data recorded in the eCRF. The data recorded should be a complete and accurate account of the subject's record, collected during the study. Subjects and male partners must not be identified in the eCRF by name or initials.

The Investigator and clinical site staff who have been delegated responsibility for entering data into the eCRF at each visit will be trained in the use of the eCRFs before being given access to the eCRF and before the first subject first visit. The Investigator must certify that the data entered into the eCRF is complete and correct.

The Investigator agrees to complete the eCRFs in a timely fashion after completion of each subject and make them available to the study monitor for full inspection. In addition, any data queries raised should be answered promptly. Following monitoring and data management review of each subject's eCRF, the Investigator will electronically sign the eCRF. Re-signature by the Investigator may be required prior to database lock after resolution of data queries identified at the data review meeting.

Before acceptance, the study monitor will review the eCRFs for completeness and adherence to the protocol. Upon completion of monitoring and once Data Management has entered data into the database, performed all edit checks, and all queries answered, the study database will be declared clean and all access will be removed.

10.2 Specification of Source Documents

Source data must be available at the clinical site to document the existence of the investigational subjects. Source data must include the original documents relating to the investigation, as well as the medical treatment and medical history of the subject. The Investigator and monitor will identify the data that will be recorded directly on the eCRF and for this data the eCRF will be considered the source document (i.e. no prior written or electronic record of the data). The monitor will confirm this at the Initiation Visit.

Source data (e.g. ICF, medical history, concomitant medication, questionnaires) contained in the subject records will be held in the ISF.

Where source data are in the form of a computer print-out (e.g. laboratory data) they will be signed and dated by the Investigator, confirming that the print-out is a true and faithful record of the data. These print-outs will be filed in the ISF.

The Investigator agrees to provide direct access to source data for investigation-related monitoring, audits, IEC / REC / IRB review, and regulatory inspection(s). Direct access to source data requires that the subject gives written, documented consent to this.

No investigation records should be destroyed without prior written agreement by the Sponsor.

10.3 Data Management

The data management group at the CRO will be responsible for eCRF development and data management activities.

Access to the eCRF will be by password and the eCRF will be backed up.

Any changes made by the Investigator and clinical site staff who have been delegated responsibility for entering data into the eCRF will be captured via an audit trail in the system.

Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the Biometrics group. The monitor is also able to raise queries in the eCRF as required.

Coding will be done manually outside of the eCRF and checked. Coding of AEs/ ADEs and medical history will be done using the most recent version of MedDRA V25.1 (or the most recent version if this has changed during the course of the clinical investigation) by the CRO.

Concomitant medications will be coded by the CRO using the latest version of the WHO dictionary (including ATC coding). All coding will be checked by the Sponsor using the most up-to-date version of MedDRA and WHO dictionary.

10.4 Reporting of CIP Deviations

Site staff should make monitor aware of any deviation from the CIP as soon as possible after occurrence. Waivers for inclusion / exclusion criteria are not allowed.

10.5 Retention of Essential Documentation

The Investigator should retain all essential documents (as defined in ICH E6 or according to other national and international regulations) until at least 10 years after the completion of the investigation (defined as last subject last visit in the investigation). These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

Subject files and other source data must be kept for the maximum period of time permitted by the Clinical Unit, hospital, institution or private practice. The Investigator must notify the Sponsor of the retention period if this is shorter than described above.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Monitoring

The Sponsor/CRO will organise regular monitoring visits to be performed at intervals agreed with the Investigator. The anticipated monitoring frequency will be stated in the Monitoring Plan. Monitoring will also involve, as appropriate, correspondence and telephone contacts.

On-site monitoring includes source data verification (SDV) which is the procedure whereby the data contained in the eCRFs are compared with the primary source data and thereby verified as accurate. It will be performed in such a way as to preserve subject confidentiality, taking into account all ethical and legislative requirements. The Investigator or designated clinical site staff, must be available at some time during the monitoring visit to review the data and resolve any queries and to allow direct access to the subject's records for SDV.

SDV will include as a minimum verification for all subjects and male partners, subject/male partner identity (age, sex and subject number), record of entry into the study and signature of the informed consent. In addition, details of SAEs in the subject's notes will be verified. Details included in the subject's notes as a minimum:

- Clinical Investigation number, brief description or title of study
- Date that the subject gave written consent
- All visit dates
- All SAEs
- All concomitant medications

At a site visit the eCRFs should be complete and available in order that the accuracy of their completion may be checked. Each completed eCRF for each subject must be signed electronically by the Investigator, to verify the data and statements submitted. Similarly, all alterations on paper

records must be initialled and dated by the Investigator or designated clinical site staff, explained as necessary, with the original mistake left legible.

11.2 Audits and Inspections

For the purpose of ensuring compliance with the CIP, ICH GCP, ISO 14155:2020 and applicable regulatory requirements, clinical studies sponsored by Reckitt may be subject to an independent audit at the investigation site which will be conducted by personnel from an appropriate Quality Assurance Unit. Full consultation with the Investigator will be made prior to and during such audit, which will be conducted according to Quality Assurance Unit SOPs.

As soon as the Investigator is notified of a planned inspection by a Regulatory Authority, he / she must inform the Sponsor promptly and allow the Sponsor to participate in the inspection as permitted by applicable regulations and local laws.

11.3 Sponsor Policy on Fraud in Clinical Studies

In accordance with GCP, it is the Sponsor's policy to always follow-up suspected cases of fraud.

12 ETHICAL AND REGULATORY ASPECTS

12.1 Ethics Review and Regulatory Authority Approval

This investigation will only be undertaken when written approval from an independent and appropriately constituted IEC/ REC/ IRB has been obtained. Documented approval must be provided to the Sponsor before any CIP related procedures.

This clinical investigation will be submitted to the Regulatory Authority (RA) and to the IEC/ REC/ IRB by the investigator/ the CRO.

The Investigator must also provide the Sponsor with a list of constituted IEC/ REC/ IRB members that includes each member's name and profession.

Any amendments to the CIP must be submitted to the RA and the constituted IEC/ REC/ IRB for approval unless where necessary to eliminate apparent immediate hazards to subjects/male partners and any administrative changes must be notified.

The Investigator or designated clinical site staff will notify the constituted IEC/ REC/ IRB within 15 days of the end of the clinical investigation (or within 24 hours if the investigation is terminated prematurely due to safety reasons).

The CRO will notify the RA within 15 days of the end of the clinical investigation (or within 24 hours if the clinical investigation is terminated prematurely due to safety reasons).

12.2 Early / Premature Termination of the Investigation

Reasons for early termination of the Clinical Investigation may include, but are not limited to:

- Recall of IP when replacements are not available.
- Unacceptable data quality.

- Withdrawal of approval from the Regulatory Authority or IEC / REC / IRB.
- Unresolved non-compliance with GCP or with the CIP that compromises the subject's/male partners rights or safety or the study data.
- Serious breach in GCP suspected or substantiated.

If the decision is made by the Sponsor to terminate the study, the Investigator at the site will be notified as soon as possible. It is the responsibility of the Investigator to ensure that the IEC / REC / IRB will be informed of the decision to terminate the study. The Investigator will also inform participating subjects/male partners that the study has been terminated, discontinue treatment (if required), and arrange for appropriate follow-up as necessary.

The Investigator will agree with the Sponsor on the fate of all Clinical Investigation materials following investigation termination.

Clinical Investigation records must be retained as noted in Section 10.5.

The Sponsor will notify the Regulatory Authority of the investigation termination.

13 COMPENSATION, INDEMNITY AND INSURANCE

13.1 Clinical Investigation Agreement

Before the investigation commences, a contract between the Sponsor and the CRO, who employs the Investigator, will be signed in which financial aspects of the study (including financial disclosure) as well as responsibilities and obligations will be described.

13.2 Insurance

If required and in accordance with applicable regulatory and legal requirements, Reckitt will take out appropriate insurance policies on behalf of the Investigator and staff who conduct part or all of this investigation and/or on behalf of the subjects participating in the investigation.

14 REPORTING, PUBLICATION AND PRESENTATION

The clinical investigation will be registered in a publicly accessible database before the start of recruitment activities in accordance with national regulations.

A CIR will be prepared according to ISO 14155:2020 (Annex D) as part of the Sponsor's commitment to GCP. The report will be a record of the total investigation conduct and findings and will be subject to approval by the Investigator who will sign the final report.

The investigation data will be owned by the Sponsor. The Sponsor retains the right to publish the data independently of the Investigator. The Sponsor agrees that before it publishes the results, it will provide the Investigator with at least 30 days for full review prior to submission of the manuscript to the publisher. The Investigator must submit any proposed manuscript to the Sponsor for approval prior to submission for publication.

15 REFERENCES

Affinito P, Palomba S, Sorrentino C, Di Carlo C, Bifulco G, Arienzo MP and Nappi C. Effects of post-menopausal hypoestrogenism on skin collagen. Maturitas 33: 239-247, 1999.

Bachmann G, Nevadunsky NS, Diagnosis and treatment of atrophic vaginitis. Am Fam Physician 61:3090-6, 2000.

Basson R, Brotto LA, Laan E, Redmond C, Utian WH. Assessment and management of women's sexual dysfunctions: problematic desire and arousal. J Sex Med, 2:291-300, 2005.

Berman JR, Adhikari SP, Goldstein I. Anatomy and physiology of female sexual function and dysfuction: classification, evaluation and treatment options. Eur Urol, 38:20-9, 2000.

Brincat M, Moniz CJ, Studd, JW, Darby A, Magos A, Emburey G & Versi E. Long term effects of the menopause and sex hormones on skin thickness. British Journal of Obstetrics and Gynaecology, 92: 256-259, 1985.

Carter J, Lachetti C, Andersen BL, Barton DL, Bolte S and Damast S. Interventions to Address Sexual Problems in Peopleith Cancer: American Society of Clinical Oncology Clinical Practice Guideline Adaptation of Cancer Care Ontario Guideline. Journal of Clinical Oncology, 36(5), 2018.

Couzi RJ, Helzlsouer KJ, Fetting JH. Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes towards estrogen replacement therapy. J Clin Oncol, 13:2737-44, 1995.

Davies SR, Guay AT, Shifren JL, Mazer NA. Endocrine aspects of female sexual dysfunction. J sex Med, 1:82-6, 2004.

Dennerstein L, Dudley EC, Hopper JL, Guthrie JR, Burger HG. A prospective population-based study of menopausal symptoms. Obstet Gynecol, 96(3):351-358, 2000.

DeRogatis L, Edelson J, Jordan R, Greenbetg S, Portman D. Bremelanotide for Female Sexual Dysfunctions: Responder Analyses from a Phase 2B Dose-Ranging Study. Poster presented at the 62nd Annual Clinical Meeting of the American College of Obstetricians and Gynecologists, 2014.

Easley EB. Sex problems after the menopause. Clin Obstet Gynecol, 21(1):269-277, 1978.

Greendale GA & Judd HL. The menopause: health implications and clinical management. J Am Geriatr. Soc 41:426-436, 1993.

Goldstein I, Alexander JL. Practical aspects in the management of Vaginal Atrophy and Sexual Dysfunction in perimenopausal and postmenopausal women.J Sex Med 2 (suppl 3) 154-165, 2005.

Hugh Hurst, Jennifer Bolton, Assessing the clinical significance of change scores recorded on subjective outcome measures. Journal of Manipulative and Physiological Therapeutics, Volume 27, Issue 1, Pages 26-35, 2004.

Kalogeraki A, Tamiolakis D, Tzardi M, et al., Cigarette smoking as a risk factor for intraepithelial lesion of the cervix uteri In vivo, 10:613-16, 1996.

Kingsberg SA, Wysocki S, Magnus L, Krychman ML. Vulvar and vaginal atrophy in postmenopausal women: findings from REVIVE (Real Women's Views of Treatment Options for Menopausal Vaginal ChangEs) survey. J Sex Med 10:1790-9, 2013.

Krychman M, Rowan CG, Allan BB, DeRogatis L, Durbin S, Yacoubian A, Wilkerson D. Effect of Single-Treatment, Surface-Cooled Radiofrequency Therapy on Vaginal Laxity and Female Sexual Function: The VIVEVE I Randomized Controlled Trial. J Sex Med, 14:215-225, 2017

Leiblum S, Bachmann G, Kemmann E, Colburn D, Swartzman L, Vaginal Atrophy in the post-menopausal woman JAMA, 249:2195-2198, 1983.

MaCoy N, Davidson J. A longitudinal study of the effects of menopause on sexuality Maturitas, 7:203-210, 1985.

Mauck, CK, Baker JM, Birnkrant DB, Rowe PJ, Gabelnick HL. The use of Colposcopy in Assessing Vaginal Irritation in Research. AIDS, 14: 2221-2227, 2000.

Nappi RE and Kokot-Kierepa M Vaginal Health: Insights, views & attitudes (VIVA) – results from an international survey. Climacteric, 15:36-34, 2012.

Nappi RE, Palacios S. Impact of vulvovaginal atrophy on sexual health and quality of life at postmenopause. Climacteric. 2014 Feb;17(1):3-9.

Notelovitz M. Gynecologic problems of menopausal women:III Changes in extragenital tissues and sexuality. Geriatrics, 33:51-53, 1978.

Palacios S. Managing urogenital atrophy. Maturitas, 63:315-18, 2014.

Panay N, Fenton A. Vulvovaginal atrophy – a tale of neglect. Climacteric 17:1-2, 2014.

Pastore LM, Carter RA, Hulka BS, Wells E. Self-reported urgogenital symptoms in postmenopausal women: Womens Health initiative Maturitas, 49: 292-303, 2004.

Recommendations related to contraception and pregnancy testing in clinical trials, Clinical Trial Facilitation Group, Version 1.1 21-Sep-2020.

Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002 Jul 17;288(3):321-33.

Sarrel PM. Sexuality in the middle years. Obstet Gynecol North Am, 14(1):49-52, 1987.

Semmens JP, Tsai CC, Semmens EC, Loadholt CB. Effects of estrogen therapy on vaginal physiology during menopause. Obstet Gynecol. 1985 Jul;66(1):15-8.

Shearer MR, Shearer ML. Sexuality and sexual counselling in the elderly. Clin Obstet Gynecol 20(1):197-209, 1977.

Simon JA, Kokot-Kierepa M, Goldstein J, Nappi RE. Vaginal Health in the United states: results from the Vaginal Health: Insights, views & Attitudes survey. Menopause; 20:1043-8, 2013.

Sodeberg MW, Brystrom B, Kalamajski S, Malmstrom A and Ekman-Ordeberg G. Gene expressions of small leucine-rich repeat proteoglycans and fibulin-5 are decreased in pelvic organ prolapse. Molecular Human Reproduction 15: 251-257, 2009.

Stenberg A, Heimer G, Ulmsten U, Cnattingius S. Prevalence of genitourinary and other climacteric symptoms in 61-year-old women. Maturitas.;24(1-2):31-36, 1996.

Steunkel CA; Davis SR: Gompel A; Lumsden MA: Murad MH; Pinkerton JV; Santen RJ. Treatment of symptoms of the menopause. An endocrine society clinical practice guideline. Journal of Clinical Endocrinology Metabolism, 100:11, 2015.

World Health Organization (WHO). Use and procurement of additional lubricants for male and female condoms: WHO/UNFPA/FHI360 Advisory Note. WHO Advisory Note. 2012;1-8.

16 APPENDICES

16.1 Appendix 1: Female Sexual Function Index (FSFI)

FEMALE SEXUAL FUNCTION INDEX (FSFI)©

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

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

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

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

TICK ONLY ONE BOX PER QUESTION

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

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

   5 ☐ = Almost always or always
   4 ☐ = Most of the time (more than half the time)
   3 ☐ = Some of the time (about half the time)
   2 ☐ = Occasionally (less than half the time)
   1 ☐ = Almost never or never

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

   5 ☐ = Very high
   4 ☐ = High
   3 ☐ = Moderate
   2 ☐ = Low
   1 ☐ = Very low or none at all

FSFI - UK/English - Final version - 17 Jan 07 - Mapi Research Institute.
[illegible]

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

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

   0 ☐ = No sexual activity
   5 ☐ = Almost always or always
   4 ☐ = Most of the time (more than half the time)
   3 ☐ = Some of the time (about half the time)
   2 ☐ = Occasionally (less than half the time)
   1 ☐ = Almost never or never

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

   0 ☐ = No sexual activity
   5 ☐ = Very high
   4 ☐ = High
   3 ☐ = Moderate
   2 ☐ = Low
   1 ☐ = Very low or none at all

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

   0 ☐ = No sexual activity
   5 ☐ = Very highly confident
   4 ☐ = Highly confident
   3 ☐ = Moderately confident
   2 ☐ = Slightly confident
   1 ☐ = Very slightly, or not confident

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

0 ☐ = No sexual activity
5 ☐ = Almost always or always
4 ☐ = Most of the time (more than half the time)
3 ☐ = Some of the time (about half the time)
2 ☐ = Occasionally (less than half the time)
1 ☐ = Almost never or never

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

0 ☐ = No sexual activity
5 ☐ = Almost always or always
4 ☐ = Most of the time (more than half the time)
3 ☐ = Some of the time (about half the time)
2 ☐ = Occasionally (less than half the time)
1 ☐ = Almost never or never

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

0 ☐ = No sexual activity
1 ☐ = Extremely difficult or impossible
2 ☐ = Very difficult
3 ☐ = Difficult
4 ☐ = Slightly difficult
5 ☐ = Not difficult

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

0 ☐ = No sexual activity
5 ☐ = Almost always or always
4 ☐ = Most of the time (more than half the time)
3 ☐ = Some of the time (about half the time)
2 ☐ = Occasionally (less than half the time)
1 ☐ = Almost never or never

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

0 ☐ = No sexual activity
1 ☐ = Extremely difficult or impossible
2 ☐ = Very difficult
3 ☐ = Difficult
4 ☐ = Slightly difficult
5 ☐ = Not difficult

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

0 ☐ = No sexual activity
5 ☐ = Almost always or always
4 ☐ = Most of the time (more than half the time)
3 ☐ = Some of the time (about half the time)
2 ☐ = Occasionally (less than half the time)
1 ☐ = Almost never or never

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

0 ☐ = No sexual activity
1 ☐ = Extremely difficult or impossible
2 ☐ = Very difficult
3 ☐ = Difficult
4 ☐ = Slightly difficult
5 ☐ = Not difficult

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

0 ☐ = No sexual activity
5 ☐ = Very satisfied
4 ☐ = Satisfied
3 ☐ = Neither satisfied/dissatisfied
2 ☐ = Dissatisfied
1 ☐ = Very dissatisfied

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

0 ☐ = No sexual activity
5 ☐ = Very satisfied
4 ☐ = Satisfied
3 ☐ = Neither satisfied/dissatisfied
2 ☐ = Dissatisfied
1 ☐ = Very dissatisfied

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

5 ☐ = Very satisfied
4 ☐ = Satisfied
3 ☐ = Neither satisfied/dissatisfied
2 ☐ = Dissatisfied
1 ☐ = Very dissatisfied

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

5 ☐ = Very satisfied
4 ☐ = Satisfied
3 ☐ = Neither satisfied/dissatisfied
2 ☐ = Dissatisfied
1 ☐ = Very dissatisfied

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

0 ☐ = Did not attempt intercourse
1 ☐ = Almost always or always
2 ☐ = Most of the time (more than half the time)
3 ☐ = Some of the time (about half the time)
4 ☐ = Occasionally (less than half the time)
5 ☐ = Almost never or never

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18. Over the past 4 weeks, how **often** have you experienced discomfort or pain <u>after</u> vaginal penetration?

0 ☐ = Did not attempt intercourse
1 ☐ = Almost always or always
2 ☐ = Most of the time (more than half the time)
3 ☐ = Some of the time (about half the time)
4 ☐ = Occasionally (less than half the time)
5 ☐ = Almost never or never

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

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

Thank you for completing this questionnaire.

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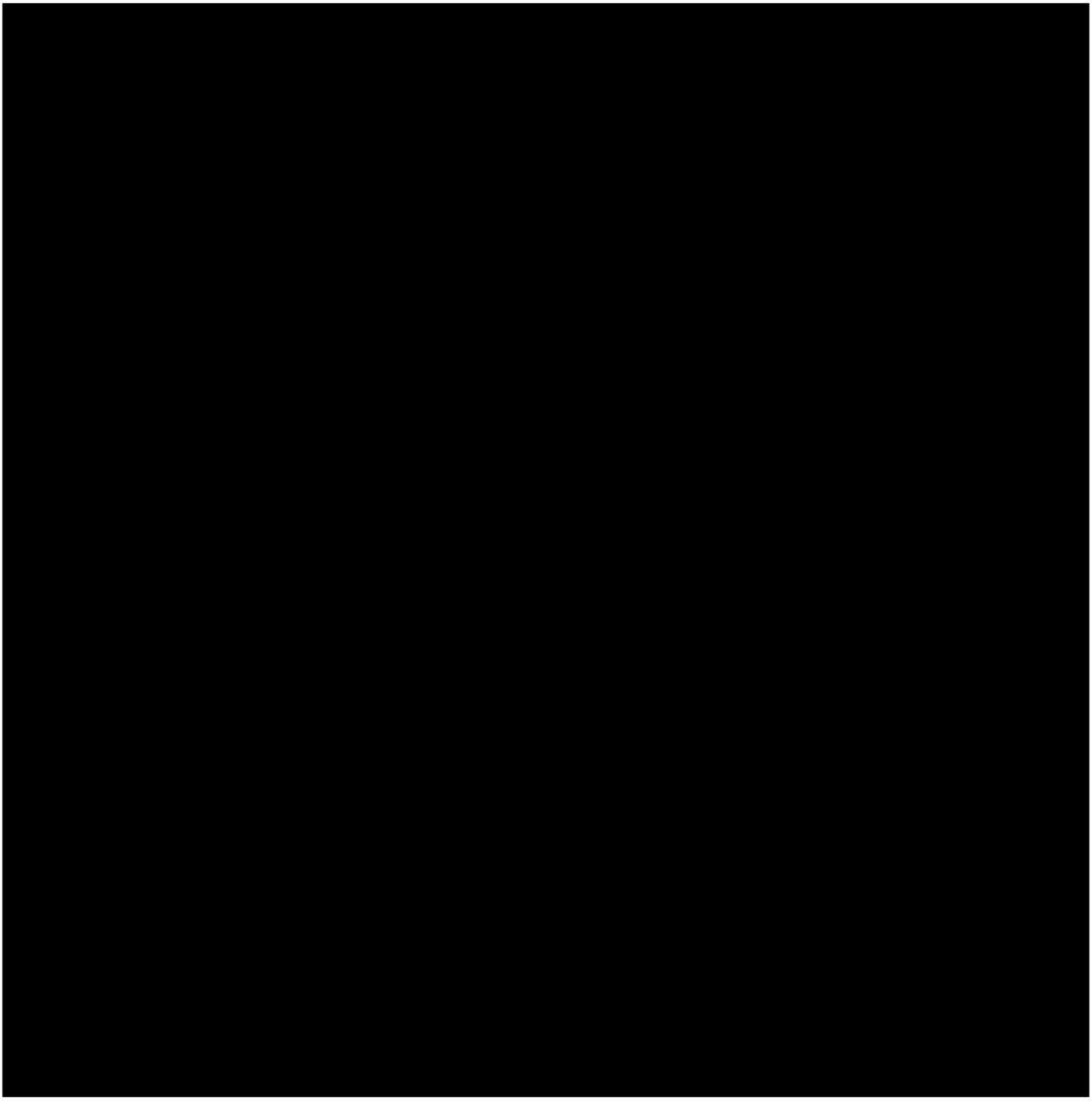

Agreement completed.

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