RECKITT

CLINICAL INVESTIGATION TITLE

A randomized, data analyst-masked, 3-way cross-over, pivotal clinical investigation to evaluate the performance of two polyurethane male condoms with different size and thickness in healthy monogamous couples during vaginal intercourse compared with a commercially available thin latex male condom.

Short Investigation Title

A 3-way crossover clinical investigation to assess the performance of two different sized polyurethane condoms versus a latex condom in healthy monogamous couples.

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Confidentiality Statement:	The information contained in this document is privileged and confidential. Do not copy, circulate or otherwise distribute without written authority from Reckitt.

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INVESTIGATOR STATEMENT

I have read and understood this Clinical Investigation Plan 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 participants 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, International Organization for Standardization (ISO) 29943-1 Condoms - Guidance on clinical studies and applicable state, local and federal regulatory requirements including United States (US) Code of Federal Regulations (CFR) applicable to clinical medical device investigations (21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21 CFR Part 11, and 21 CFR Part 812) .
- to conduct this investigation only after a favourable opinion is obtained from the Institutional Review Board (IRB)/Central Institutional Review Board (CIRB) and Regulatory Authority (RA-if required).
- to ensure that data collected during this investigation is accurate, complete and recorded in a manner that is consistent with the CIP and regulatory requirements.
- to ensure that informed consent from each participant participating in this investigation is obtained in writing before the participant enrols in the investigation, as outlined in 21 CFR Part 50.
- to ensure all investigation personnel are adequately trained and delegated tasks commensurate with their qualifications.
- to disclose any financial interests that could interfere with the conduct of the clinical investigation.
- to report all information or data in strict 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.

- that failure to comply with any of the above commitments may result in penalties as stipulated by law.

I have read and understood the responsibilities that are expected of me as the Principal Investigator for this clinical investigation.

By signing below, I affirm my commitment to adhere to the aforementioned regulations and responsibilities for the duration of the clinical investigation.

Principal Investigator
(Reviewed and Accepted):

_____ _____

Terri Walsh MPH Date
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LIST OF ABBREVIATIONS

Abbreviation	Abbreviation in Full
ADE	Adverse Device Effect
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
CFR	Code of Federal Regulations
CI	Confidence Interval
CIP	Clinical Investigation Plan
CIRB	Central Institutional Review Board
CRO	Clinical Research Organisation
DCT	Decentralised Clinical Trial
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eISF	Electronic Investigator Site File
ePRO	Electronic Patient Reported Outcome
EMSEX	Event-Level, Male Sexual Pleasure Scale
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalised Estimating Equations
GMP	Good Manufacturing Practice
GP	General Practitioner
GVG	Global Vigilance Group
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus

Abbreviation	Abbreviation in Full
HSV	Herpes Simplex Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
IMSU	Investigational Materials Supplies Unit
IP	Investigational Product
IRB	Institutional Review Board
ISF	Investigator Site File
ISO	International Organization for Standardization
NI	Non-Inferiority
NIP	Non-investigational Product
NMAR	Not missing at random
NRL	Natural Rubber Latex
PCP	Primary Care Physician
PIL	Patient Information Leaflet
PP	Per Protocol
PU	Polyurethane
QSE	Quality of Sexual Experience
RA	Regulatory Authority
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDR	Source Data Review
SDV	Source Data Verification
SOP	Standard Operating Procedure
STI	Sexually Transmitted Infection

Abbreviation	Abbreviation in Full
TEAE	Treatment-Emergent Adverse Event
TEADEs	Treatment-Emergent Adverse Device Effects
USADE	Unanticipated Serious Adverse Device Effect

CLINICAL INVESTIGATION SYNOPSIS

Investigation Title:	A randomized, data analyst-masked, 3-way cross-over, pivotal clinical investigation to evaluate the performance of two polyurethane male condoms with different size and thickness in healthy monogamous couples during vaginal intercourse compared with a commercially available thin latex male condom.
Reckitt Investigation Number:	2628301
Background and Rationale:	The Natural Rubber Latex (NRL) male condom is a widely used method of contraception and has a well-established long history of its safety and effectiveness. However, the key limitation is its potential to induce an allergic reaction or to create latex sensitivity with repeated use. This has led consumers to seek alternatives to the latex condom, made from non-latex materials, that are non-allergenic or do not create sensitisation. To enhance the sensory experience in a more comprehensive way and address the specific consumer needs, the Sponsor has developed new Polyurethane (PU) male condoms with 57 ± 2 mm width, 30 ± 5 µm thickness and 63 ± 2 mm width, 35 ± 5 µm thickness. This clinical investigation is designed in accordance with ISO 29943-1:2017 Condom – Guidance on clinical studies as a pivotal investigation to assess the safety and performance of two different PU condoms in the USA. The rates of condom ‘slippages and breakages’ are internationally recognised as two measures of performance when evaluating both latex and non-latex condoms. The main aim of this investigation is to determine the performance, through total clinical failure (combined slippage and breakage) rate of two PU male test condoms with different thickness and size compared to a commercially available NRL male control condom (57 ± 2 mm width, 50 ± 2 µm thickness).

Objectives:	Primary Objectives: • To evaluate the performance (total clinical failure) of PU male test condom (Test condom 1) compared with the NRL male control condom during vaginal intercourse in healthy monogamous couples. • To evaluate the performance (total clinical failure) of PU male test condom (Test condom 2) compared with the NRL male control condom during vaginal intercourse in healthy monogamous couples. Secondary Objectives: • To evaluate the clinical breakage and clinical slippage respectively of the PU male test condom (Test condom 1) compared with the NRL male control condom when used during vaginal intercourse in healthy monogamous couples. • To evaluate the clinical breakage and clinical slippage respectively of the PU male test condom (Test condom 2) compared with the NRL male control condom when used during vaginal intercourse in healthy monogamous couples. • To evaluate the non-clinical breakage and non-clinical slippage respectively of each PU male test condom and the NRL male control condom when used during vaginal intercourse in healthy monogamous couples. • To evaluate the user acceptability of the 2 PU male test condoms and the NRL male control condom. • To evaluate the in-use tolerability of the 2 PU male test condoms and the NRL male control condom. • Safety Objective: • To assess the safety of the 2 PU male test condoms and the NRL male control condom. • Exploratory Objectives: • To evaluate total clinical failure, clinical breakage, clinical slippage, non-clinical breakage, and non-clinical slippage rates in users according to whether additional lubricant was used. • To evaluate sexual pleasure during the use of 2 PU male test condoms and NRL male control condoms via EMSEX pleasure scale and Quality of Sexual Experience (QSE) Scale. • To evaluate correlations among size, fit, and performance of the 2 PU male test condoms and NRL male control condom, including factors of erect penile size (length and girth), user condom size preference

	(previous of and during the investigation), size of each condom type used in the investigation (PU male test and NRL male control condom), comfort/fit with condoms, and condom performance (total clinical failure, clinical breakage, clinical slippage, non-clinical breakage, and non-clinical slippage rates).
Primary Endpoint:	• The total clinical failure rate (combined breakage and slippage) of PU male test condom (Test condom 1) compared to the NRL male control condom. • The total clinical failure rate (combined breakage and slippage) of PU male test condom (Test condom 2) compared to the NRL male control condom.
Secondary Endpoints:	• The total clinical breakage rate of the PU male test condom (Test condom 1) compared to the NRL male control condom. • The total clinical slippage rate of the PU male test condom (Test condom 1) compared to the NRL male control condom. • The total clinical breakage rate of the PU male test condom (Test condom 2) compared to the NRL male control condom. • The total clinical slippage rate of the PU male test condom (Test condom 2) compared to the NRL male control condom. • The total non-clinical breakage rate for each of the PU male test condoms and the NRL male control condom. • A measure of the total non-clinical slippage rate for each of the PU male test condoms and the NRL male control condom. • User acceptability, experience, and preference of each condom type will be evaluated through participant perceived questions. • In-use tolerability of each condom type will be evaluated through participant perceived questions.
Safety Endpoints:	Overall proportion of participants with Adverse Events / Adverse Device Effects (AEs/ADEs), i.e., the occurrence of one or more AEs/ADEs per participant.

Exploratory Endpoints:	• For each condom type:
	  ○ The total clinical failure rate by whether additional lubricant was used or not used.
	  ○ The total clinical breakage rate by whether lubricant was used or not used.
	  ○ The total clinical slippage rate by whether additional lubricant was used or not used.
	  ○ The total non-clinical breakage rate by whether additional lubricant was used or not used.
	  ○ The total non-clinical slippage rate by whether additional lubricant was used or not used.
	• The total clinical failure rate (combined breakage and slippage) of PU male test condom (Test condom 2) compared to the NRL male control condom for participants in Penis Size Category 1 (mid shaft lower limit greater than or equal to 128mm).

Success Criteria:	ISO 29943-1:2017 Condoms – Guidance on clinical studies for the primary endpoint requires an upper one-sided 95% confidence limit for total clinical failure rate (combined breakage and slippage) of the PU male test condoms minus Natural Rubber Latex (NRL) male control condom to be less than 2.5%. To control the overall type 1 error rate at ≤5%, non-inferiority will be concluded if the upper one-sided 97.5% confidence limit is 2.5%, if the upper one-sided 97.5% confidence limit is above 2.5% then the investigation will have failed to demonstrate non-inferiority. If only one comparison is non-inferior, then the investigation will be considered to be a partial success.
Design:	This is a randomised, data analyst-masked, 3 way cross-over pivotal clinical investigation to compare the performance (clinical failure rate) of two different sized PU male test condoms and the commercialized NRL male control condom based on the guidance set out in ISO 29943-1:2017 Condoms – Guidance on clinical studies.

Participants:	The aim is to enrol 300 monogamous heterosexual couples into the study in order for 256 couples to complete the investigation, with the aim of ensuring a minimum of 1000 uses of each condom type. **Inclusion Criteria** 1. Both partners participating must provide written informed consent. 2. Couples must include a male and female within a heterosexual couple and be between 18 – 60 years of age inclusive. 3. Both partners must be willing to respond to questions about their reproductive and contraceptive history and use of condoms during interviews and respond to self-administered questionnaires as per instructions. 4. Both partners must agree to answer the questions in the condom use questionnaires and two scales as soon as possible and within 2 (+6) hours following each coital act. 5. Both partners must be generally healthy and in a mutually monogamous heterosexual relationship - current relationship ≥ 3 months. 6. All couples must be averaging one act of intercourse weekly, agree to have penile-vaginal intercourse with a frequency sufficient to meet CIP requirements. 7. The female partner must also use an established (as agreed by the Investigator) other highly effective form of non-barrier contraception, unless post-menopausal. 8. Both partners must be able to understand instructions for correct use of condoms. 9. Both partners must have an adequate level of literacy to understand and to be able to answer the questionnaires. 10. Both partners must agree to use only the investigational condoms during the time of participation. 11. Participants must agree to use the penis measuring kit provided to measure the erect penis at investigation start. 12. Both partners must agree not to use drugs or non-investigational devices that can affect sexual performance. 13. Both partners must have no known sexually transmitted infections including Human Immunodeficiency Virus (HIV) / acquired immune deficiency syndrome (AIDS) (medical history via self-report)(uncomplicated Herpes simplex virus (HSV) and positive

	Human papillomavirus (HPV) which are asymptomatic may be included in the investigation in the opinion of the Investigator). 14. Both partners must agree to use only lubricant(s) provided for the duration of investigation. 15. Both partners must agree not to wear any genital piercing jewellery for the duration of the clinical investigation. 16. Both partners must have no past medical history of any health condition (self-reported) that, in the opinion of the Investigator, would be considered clinically relevant. 17. Couples must have a compatible electronic device with internet access which they are willing to upload questionnaire data to the web-based platform throughout the investigation. 18. Both partners will be available for follow-up. **Exclusion Criteria** 1. Either partner is or becomes aware of an allergy or sensitivity to the ingredients of any of the products. 2. Either partner has been receiving daily treatment for their pre-existing skin condition (for example, severe eczema/psoriasis) within the three months prior to the screening for this study. 3. Female partner that is pregnant or desires to become so while participating in investigation. 4. Any couple undergoing any form of fertility treatment. 5. Either partner needs to use condoms for sexually transmitted infection (STI) protection. 6. Either partner has previous or planned genital surgery that in the opinion of the Investigator would consider the participant unsuitable to participate in the clinical investigation. 7. Either partner are commercial sex workers. 8. Either partner are itinerant persons who will be unable to complete the clinical investigation. 9. Couples that in the opinion of the Investigator, would be unable to complete the investigation. 10. Male partners that have known erectile or ejaculatory dysfunction in the past month. 11. Either partner requires to use/ is using medication or preparations that are applied topically to the genitalia area or intravaginally, other than that supplied for the investigation.

	12. A female partner that has been diagnosed with or treated for vaginal complaints (including vaginal dryness) in the previous 3 months which, in the opinion of the Investigator, deems the partner unsuitable for the investigation. 13. Either partner uses any medication which in the Investigator's opinion may interfere with the use of condoms. 14. A male partner with abnormal penile anatomy or genital lesion that would, in the opinion of the Investigator, affect the ability to keep the condom in place during intercourse. 15. Either partner is suffering from any health conditions (self-reported) or any condition which could, in the opinion of the Investigator, affect the outcome of the investigation or affect their safety if they participate. 16. Either partner have participated in a clinical trial in the previous month which could, in the opinion of the Investigator, affect the outcome of the investigation. 17. Either partner is an employee of the investigational Sponsor or affiliated with the clinical research centre. 18. Either partner has a recent history of drug/alcohol abuse within the previous 12 months. 19. Either partner has an inability to follow the procedures of the investigation. 20. Either partner is unable, in the opinion of the Investigator, to fully comply with the investigation requirements.

Product(s) to be Evaluated and Treatment Regimen:	**Investigational products:** Three male condoms (2 test and 1 control male condom) to be evaluated are: <u>Test Products:</u> • Test condom 1: Polyurethane male condom with 57 ± 2 mm width, 30 ± 5 µm thickness • Test condom 2: Polyurethane male condom with 63 ± 2 mm width, 35 ± 5 µm thickness <u>Control Product:</u> • Natural Rubber Latex (NRL) male condom with 57 ± 2 mm width and 50 ± 2 µm thickness **Non investigational products (non-IP):** Lubricant is applied to the test condoms and control condom before packaging. However, couples may desire additional lubricant, as standard, KY True Feel Lube will be supplied. **Test regimen:** Couples will be randomised into using one of the three condoms for a minimum of 5 uses over a 5-week assessment period. Then they will repeat the 5-week assessment period twice more for the two remaining condoms. Additional lubricant (non-investigational product) will be provided to all participants for use during intercourse, if desired.

Methodology:	This clinical investigation will be conducted via a Decentralised Clinical Trial (DCT) approach, where all visits will be conducted virtually via teleconference/video call or phone calls except for curbside visits and emergency situations or adverse event assessments which may require a participant to be seen and assessed at an emergency hospital or at a private clinic. The aim is to enrol 300 healthy monogamous heterosexual couples remotely from three different geographic locations by one investigational site. Recruitment locations were selected based on population diversity with respect to ethnicity and socio-economic groups. There will be 3 remote visits (Visit 0, Visit 1 and Visit 6) via teleconference/video/phone call and 4 curbside visits (Visit 2-Visit 5). Curbside visits will be arranged for delivery and collection of the study supplies at a suitable prearranged location (e.g., clinic parking lot, library) which ensures safety for both the participants and delegated site staff during the exchange of study materials e.g., IP, Non-IP (lubricant), pregnancy test kit, penis measuring kit. Curbside visits will be arranged by the delegated site staff via video conference/phone calls/text messages prior to each visit. Additional phone contacts will be conducted prior to each curbside visit as needed. The duration of the clinical investigation is anticipated to be approximately 19 weeks (from screening to exit phone visit). **Visit 0: Consent and Instruction Visit- Within 7 (+7) days prior to Day 1** The informed consent process will be conducted remotely via videoconference with both partners. Before undergoing any clinical investigation procedure, each partner will be asked to provide written informed consent for their participation in the clinical investigation. After obtaining the consent, participants will be trained on how to use a condom and penis measuring kit and how to enter the data into the web-based platform. Both partners will be provided with login details to access the Study Entry Questionnaire (SEQ). The couple will be instructed to complete a Condom Use Questionnaire together for each condom used, an EMSEX pleasure scale by the male

	participant and QSE scale separately by each partner for each condom as soon as possible and within 2 (+6) hours after each coital act. Couples will also be instructed to examine the condom carefully when removing the condom from the penis, for breakages. All breakages and slippages are to be recorded on a Condom Use Questionnaire. **Visit 1: Screening Phone Visit – Within 7 (+7) days prior to Day 1** The screening visit procedures will consist of inclusion/exclusion criteria, concomitant medications, medical history, demographics, study entry questionnaire and instructions for female partner on how to perform the pregnancy test and how to enter the results on the web-based platform. If both partners meet all inclusion and exclusion criteria, the couple will be scheduled for their first curbside visit. A urine pregnancy test kit will be provided to female participants. Eligible couples will be classified into Group A or Group B based on male participant's answers to relevant questions in the Study Entry Questionnaire using Appendix 1. Adverse Events (AEs), concomitant medications and products will be collected from the start of the screening visit until the exit visit. **Assessment Period 1** **Visit 2: First Curbside Visit - Day 1** Eligibility for entry onto the clinical investigation will be reconfirmed. Following confirmation that the female partner has entered a negative pregnancy test result into the web-based platform, the couples will be randomised into using one of the three condoms for a minimum of 5 uses over a 5-week (Assessment Period). Both partners must provide official government-issued photo identification to re-verify their identity before they can receive any study materials. The delegated site staff must also show their company card Identification Document (ID). Couples will be given a carton containing their first set of condoms, the penis measuring tool and will be asked to complete the Condom Use Questionnaire and scales as described at Visit 0. Eligible couples will be classified into Penis Size Category 1 (penis mid-shaft girth size is ≥128mm) or Penis Size Category 2 (penis mid-shaft girth size is <128mm) based on the data derived from the penis measuring tool, see Appendix 2. After completing each assessment period, couples will be required to complete the End of Condom Use Period Questionnaire.

	Assessment Period 2 and 3 **Visits 3 and 4: Second and Third Curbside Visit- within 7 (+7) days after each assessment period** In advance of each visit, completion of questionnaires and scales will be reviewed by the delegated staff. If necessary, further training on the clinical investigation requirements will be given. During telephone visits, AEs, concomitant medications and products will be recorded and updated for each partner. Procedures and assessments performed during visit 3 and visit 4 will be the same as those performed during Assessment Period 1, except for randomisation, providing pregnancy test results and penis measuring kit delivery related activities. Couples will be required to return all unused condoms of the first and second condom type from Assessment Periods 1 and 2 at the second and third curbside visits (Visit 3 and Visit 4), respectively. **End of Assessment Period 3** **Visit 5: Fourth Curbside Visit- within 7 (+7) days after third assessment period** Couples will be required to return their unused condoms (3rd condom type) and unused additional lubricants. Female partner will be provided a pregnancy test kit. **Visit 6: Exit visit - within 7 (+7) days after third assessment period and visit 5** The exit visit will be conducted via phone after the completion of the third Assessment Period and visit 5, or in the event of a couple's early withdrawal from the clinical investigation. AE and concomitant medication information will be collected. Female participants will be requested to take a urine pregnancy test at home and provide the results in advance of the visit.

Statistical Evaluation:	There are two primary endpoints of the investigation: • The total clinical failure rate of the PU male test condom 1 compared to the NRL male control condom. • The total clinical failure rate of the PU male test condom 2 compared to the NRL male control condom. The clinical failure rate is calculated as the number of condoms with at least 1 acute failure event (e.g., clinical slippage or clinical breakage) divided by the number of condoms used during intercourse. The clinical failure rate will be reported as a percentage. A condom that experiences multiple clinical failure events only counts as a single clinical failure. Both two test PU male condoms must be non-inferior to NRL male control condom with a non-inferiority margin of 2.5%. If only one comparison is non-inferior then the investigation will be considered to be a partial success. For the primary endpoint, each condom usage during vaginal intercourse will be considered either a clinical success or a clinical failure. It will be considered a clinical failure if either the condom breaks or tears during intercourse or withdrawal from the vagina, or the condom slips off completely during intercourse or during withdrawal from the vagina. Since the outcomes of each condom use by a particular couple are expected to be more alike than the outcomes of condom use by another couple, this within-couple correlation should be accounted for in the analysis. A generalised estimating equations (GEE) model with an identity link function and independent working correlation structure will be used to analyse the total clinical failure rate. Covariates will include condom type (i.e., treatment), location and investigational period. Interactions between condom type and centre will be investigated, and if found to be non-significant at the 10% level of significance ($p>0.1$), the interaction term will be dropped from the final model. If an interaction is detected, then further analyses will be performed to understand the nature of the interaction and the results will also be presented separately for each investigational location. From the GEE model, the difference in the proportion of condoms experiencing failure in the test and reference condoms will be presented together with an upper one-sided 97.5% confidence interval. If the upper limit is less than 2.5%, this will provide sufficient evidence that the test condom is non-inferior to the NRL control condom with respect to clinical failure.

	If non-inferiority is achieved, a test of superiority can then be performed. As per ISO 29943-1:2017 Condom – Guidance on clinical studies, in order to declare superiority, the upper limit of the one-sided 97.5% confidence interval will need to be <0%. Further details also relating to the secondary endpoints analysis are provided in the statistical sections.

1. BACKGROUND AND RATIONALE

1.1 Background for the Investigation and Rationale

The Natural Rubber Latex (NRL) male condom is a widely used method of contraception and has a well-established long history of its safety and effectiveness. However, the key limitation is its potential to induce an allergic reaction or to create latex sensitivity with repeated use. This has led consumers to seek alternatives to the latex condom, made from non-latex materials, that are non-allergenic or do not create sensitisation.

Ideally the non-rubber latex condom alternative, such as the Polyurethane (PU) condom, would provide protection from sexually transmitted infection (STI) and unintended pregnancy whilst also being non-allergic, aesthetically pleasing, have thinner characteristics and offer good performance to condom users. From a public health perspective, a male condom that addresses the limitations of existing latex products may be the most promising approach to promote increased condom usage.

To enhance the sensory experience in a more comprehensive way and address the specific consumer needs, the Sponsor have developed new PU male condoms with 57 ± 2 mm width, 30 ± 5 µm thickness and 63 ± 2 mm width, 35 ± 5 µm thickness.

This investigation is planned as a pivotal investigation to assess the safety and performance of two different PU condoms in the USA.

The main aim of this investigation is to determine the performance, through total clinical failure (combined slippage and breakage) rate of two PU male test condoms with different thickness and size compared to a commercially available NRL male control condom (57 ± 2 mm width, 50 ± 2 µm thickness). The secondary aim of this investigation is to evaluate the performance (clinical slippage and clinical breakage respectively compared to NRL male control condom), the non-clinical breakage and non-clinical slippage respectively for each of the two PU male test condoms and the NRL male control condom and the safety of the two PU male test condoms and the NRL male control condom during vaginal intercourse. This investigation will also evaluate the user acceptability and the in-use tolerance of the PU male test and control condoms in both male and female participants.

1.2 Investigational Products

All condoms, used in this clinical investigation, have been formulated using well recognised ingredients with good safety profiles and the risks associated with the design and formulation of the product are minimal. Furthermore, the investigational products to be used in this clinical investigation have been manufactured to Good Manufacturing Practice (GMP) requirements as per ISO 23409 Male condoms – Requirements and test methods for condoms made from synthetic materials, ISO 4074 Natural latex rubber condoms – Requirements and test methods and ISO 13485 Medical devices – Quality management systems – Requirements for regulatory purposes.

Test Products

In this investigation, two Polyurethane (PU) male condoms of varying thickness and size are to be evaluated:

- Test male condom 1: 57 ± 2 mm width, 30 ± 5 µm thickness
- Test male condom 2: 63 ± 2 mm width, 35 ± 5 µm thickness

Control Product:

Natural Rubber Latex (NRL) male condom (57 ± 2 mm width and 50 ± 2 µm thickness) is selected as the control condom. It is commercialized in the USA, as one of the current thinnest Durex NRL condom variants with a comparable thickness feature to the test products, launched as large size NRL condom with comparable width to both of the test products. This control product selected via following the ISO: 29943-:2017 (Condoms — Guidance on clinical studies) guidance.

Details of the investigational products are provided in Section 5.1.

1.3 Treatment Rationale

The ISO 29943-1:2017 Condoms- Guidance on clinical studies has been followed to design this investigation and the use of condoms. To determine the performance, the PU male condoms with two different sizes (Test product 1: 57 ± 2 mm width, 30 ± 5 µm thickness and Test product 2: 63± 2 mm width, 35 ± 5 µm thickness) will be tested against the NRL male control condom (57± 2 mm with, 50 ± 2 µm thickness) in a 3-way cross-over design. Couples will be randomised into using one of the three condoms for a minimum of 5 uses over a 5-week assessment period, then will repeat the 5-week assessment period twice more for the two remaining condoms. All condoms will be used as instructed during vaginal intercourse as per ISO 29943-1:2017 Condoms – Guidance on clinical studies.

1.4 Investigation Population and Indication

The target population will be healthy male and female participants who are in a mutually monogamous heterosexual relationship (for ≥3 months).

The males within each couple will represent potentially different penis sizes.

Couples (one male and one female partner) will be classified into either Penis Size Category 1 (which is a group of participants whose penis mid-shaft girth size is ≥ 128mm) or Penis Size Category 2 (which is a group of participants whose penis mid-shaft girth size is <128mm) using data derived from the penis measuring tool. For details on how participants are classified into either Penis Size Category 1 or 2, please refer to Appendix 2 - Assignment of Penis Size Category.

The target proportion for each Penis Size category is approximately 150 couples, with a flexibility of ± 30 couples (approximately 120 couples in one Penis Size category, with 180 couples in the other Penis Size category) however, recruitment will continue until 300 couples have been enrolled.

Participants will be recruited and enrolled from three distinct geographic locations in order to enhance the diversity of the investigation population, selected via the review of each location's demographics, including population, age, sex, race (and Hispanic origin), housing, computer and internet usage, income and poverty (data will be assessed via https://www.census.gov). This decentralized approach will be enabled through the use of electronic systems (e.g., eConsent, ePRO) and direct delivery of investigational product to participants, removing the requirement for participants to travel to site. Participants will be trained and supported in the use of these systems throughout the investigation by site personnel.

1.5 Non-Clinical Evidence

The test products have been assessed in line with the regulatory classification for these product type.

Non-clinical evidence is summarised in Section 2 of the IB. The main points are as follows:

A risk management process has been used to evaluate and test the medical devices in a non-clinical setting. This process reviewed the physical and chemical characteristics of the various materials, any existing toxicology, other biological safety data on the product, and the biocompatibility tests on the component materials.

On the basis of the available toxicological, and safety data for the ingredients, the 2 PU male condoms are considered suitable for further development for their intended and foreseeable conditions of use when used in accordance with the product label. Overall, the investigational PU condoms pose no significant toxicological concerns. The results of the testing demonstrate no adverse toxicological effects in the relevant biological endpoints.

1.6 Clinical Evidence to Date

The following testing and experimental data have been gathered on the investigational devices or similar products as part of the clinical evaluation. There is no clinical data available on the investigational devices, therefore data presented are from similar devices.

A clinical investigation has been conducted on a similar PU condom on behalf of the manufacturer and is referenced in the following Section 1.6.1.

1.6.1 Clinical Investigation on Polyurethane and Natural Rubber Latex Condoms

Reckitt Study Number 1003201: A randomised, assessor masked, 2-way cross-over clinical investigation was conducted to evaluate the performance rate of a 25µm PU condom in healthy

monogamous couples during vaginal intercourse when compared to a 55µm standard latex condom. The investigation was based on the guidance set out in ISO 29943-1:2017 Condom – Guidance on clinical studies. A total of 235 couples were planned for enrolment, 238 were screened, 235 randomised, and 231 completed the Clinical Investigation. The PU condom evaluated in the clinical investigation has the same formulation as the 2 PU condoms included in this clinical investigation 2628301 (Reckitt Study Number). Differences between condom dimensions and lubricant are detailed in Table 1-1.

Table 1-1 Comparison of Condom Dimensions and Lubricant Volume Between the Proposed Reckitt Study 2628301 and the Previous Reckitt Study 1003201

Reckitt Study Number	**Condom material**	**Condom Reference**	**Length (mm)**	**Width (mm)**	**Thickness (µm)**	**Lubricant level (mg)**
2628301	PU	PUCON10/PULUB4 (PIBOM 3243906)	185 ± 10	57 ± 2	30 ± 5	minimum 700 mg
	PU	PUCON9/PULUB5 (PIBOM 3247902)	185 ± 10	63 ± 2	35 ± 5	minimum 800 mg
	NRL	CON73/LUB7 (GPA50008601)	190 ± 10	57 ± 2	50 ± 2	480 ± 50
1003201	PU	Test condom (PU condom)	180 ± 10	54 ± 2	25 ± 5	minimum 600 mg
	NRL	Reference Condom (NRL Condom)	180 ± 10	52 ± 2	55 + 4/-8	400 ± 50

The primary outcome measure was total clinical failure (clinical breakage and clinical slippage) rate. The primary analysis (and the confirmatory evaluation for the investigation) was the comparison between test (PU) and reference (NRL) condoms.

For the primary endpoint analysis of clinical failure in the full analysis set (FAS), the upper limit of the one-sided 95 % CI was 1.78 % (i.e., less than the 2.5 % non-inferiority margin), which demonstrated sufficient evidence that the 25µm PU condom (test condom) was non-inferior to the 55µm NRL condom (reference condom), with respect to clinical failure. The upper limit of the one-sided 97.5 % CI was 1.94 % (i.e., not less than 0 %), which did not show superiority between 25µm PU condom (test condom) and 55µm NRL condom (reference condom), with respect to clinical failure. The clinical failure rate in the test PU condom was 3.60 % (95 % CI: 2.62 % to 4.82 %). The clinical failure rate in the reference NRL condom was 2.43 % (95 % CI: 1.63 % to 3.47 %), which was within the expected range of 0.5 % -4.0 %, confirming the investigation validity in terms of the clinical failure rate in the NRL condom. Similar results to that of FAS were observed for primary endpoint analysis in the Per Protocol (PP) set.

For the secondary endpoint analysis of clinical breakage, the 25µm PU condom (test condom) was not shown to be non-inferior to the 55µm NRL condom (reference condom). However, a sensitivity analysis of clinical breakage was performed with 1 record (206-010) for which both Condom Use Questionnaire as well as lab data were missing removed from the analysis. Based on the sensitivity analysis, the upper limit of the one-sided 95 % CI was 1.96 % (i.e., less than the non-inferiority margin 2.0 %), which showed that the 25µm PU condom (test condom) was non-inferior to the 55µm NRL condom (reference condom), with respect to clinical breakage.

The 25µm PU condom (test condom) was shown to be non-inferior to the 55µm NRL condom (reference condom) with respect to clinical slippage, with the upper limit of the one-sided 95 % CI to be 0.95 % (i.e., less than the non-inferiority margin 2.0 %).

The 25µm PU condom (test condom) had a similar safety and tolerability profile when compared to the 55µm NRL condom (reference condom). Overall, 15/234 (6.4%) female and 4/234 (1.7%) male participants reported at least 1 treatment-emergent adverse event (TEAE), with a total of 22 events and 4 events reported respectively. There were no severe TEAEs, serious TEAEs, or related TEAEs reported in both female and male participants. Two (0.9%) female participants reported 2 related treatment-emergent adverse device effects (TEADEs) (device allergy in 55µm NRL condom and genital rash in 25µm PU condom) that led to participant withdrawal. Genital rash (mild in severity) was possibly related to the investigational device by the Investigator, and the device allergy (moderate severity) was considered to have causal relationship to the investigational device by the Investigator. One (0.4%) male participant reported 1 related TEADE (genital rash in 25µm PU condom) that led to participant withdrawal. Genital rash (mild in severity) was possibly related to the investigational device by the Investigator. There were no severe TEADEs, or serious TEADEs reported in both female and male participants. Overall, there were no clinically significant abnormalities in vital signs or physical findings which met the criteria of an AE. The 25µm PU condom also performed well in assessments of user acceptability, experience, preference, and in-use tolerability. In conclusion, the 25µm PU condom was shown to be non-inferior in performance to the 55µm NRL condom when considering clinical failure rate and is demonstrated to be safe and well tolerated.

1.6.2 Clinical Data from Scientific Literature

A systematic review of the clinical literature has been conducted to identify any potential sources of clinical data relevant to the PU investigational devices. A review of the published literature is presented hereafter.

1.6.2.1 Clinical Effectiveness

A literature review was conducted for the clinical evaluation of the PU condoms within the scope of this clinical investigation in June/July 2023. During this review, a total of 12 publications were identified as relevant to the evaluation of PU condom effectiveness. Table 1-2 summarises the rates of breakage and slippage as reported in published clinical trials.

Table 1-2 PU Condom Breakage, Slippage and Failure Rates Reported in the Literature

Study reference	Condoms tested	Clinical breakage*		Clinical slippage / severe slippage (>1 inch)	
		%	95% CI	%	95% CI
Bounds et al., 2002	eZ·on PU condom	3.7	Not specified	2.4	Not specified
	Avanti PU condom	2.9	Not specified	2.9	Not specified
Steiner et al., 2003	eZ·on PU condom	3.8	Not specified	4.9	Not specified
Cook et al., 2001	eZ.on PU and latex condoms	5.6	0.87	1.6	0.36
Frezieres et al., 1999	Ramses Sensitol (NRL) and PU condom	4.3	Not specified	4.5	Not specified
Frezieres et al., 1998	Avanti PU condom	7.2	Not specified	3.6	Not specified
Frezieres & Walsh, 2000	Trojan Enz, PU and SEBS condoms	2.0	Not specified	3.3	Not specified
Farr et al., 1997	Prototype PU condom	1.9	0.9 – 3.5	3.7	2.2 – 5.7
Potter & Villemeur, 2003	Sagami Latex condom vs PU	0.6	0.2 – 1.4	1.1	0.5 – 1.9
Rosenberg et al., 1996	Avanti PU condom (5 studies)	0.9 1.7 2.1 1.1 0.3	Not specified	1.3 2.4 1.0 1.1 1.3	0.5 – 2.8 1.2 – 4.2 0.3 – 2.4 0.4 – 2.4 0.6 – 2.5
NCT04622306, 2023	Not identified PU and latex condoms	1.3 (PU condom A) 1.9 (PU condom B)	Not specified	1.1 (PU condom A) 1.1 (PU condom B)	Not specified

CI: Confidence Interval

*number of condoms broken during intercourse or withdrawal divided by the number of condoms used during intercourse

Further to the primary publications summarised above, Gallo et al. (2003) and Gallo et al. (2006) performed systematic reviews and meta-analysis of condom failure rates comparing synthetic PU versus latex condoms (Gallo et al., 2003; Gallo et al., 2006). The latest analysis (2006) included 11 studies: Eight randomised crossover trials (Bounds 2002; Callahan 2000; Cook 2001; Frezieres 1998; Frezieres 2000; Potter 2003; Steiner 1993 and Trussell 1992) and three randomised parallel trials (Frezieres 1999; Nelson 2001 - published in Walsh et al., 2003 - and Steiner 2003). Most of the trials have been identified and summarised in the table above. Reported clinical failure rates for both latex and synthetic condoms ranged from an odd ratio of 2.64 (95% CI 1.63-4.28) to 4.95 (95% CI 3.63-6.75). The authors concluded that synthetic condoms displayed similar failure rates as reported in the broader clinical literature, however in the studies analysed they did appear to have a higher chance of breakage compared to latex varieties. Despite this, the overall clinical failure rates were relatively low and demonstrated non-latex condoms be an acceptable alternative for those with sensitivities, aversion, or reluctance to the use of latex condoms. Study limitations were noted with variability in condom familiarity and definition of “experienced” condom users between the studies; methodological limitations in the analysis of cross-over trial data as parallel data, undermining the ability of cross-over data to control for within-participant correlations and maintain statistical independence of the data; the reliance on self-reported outcomes and the fact that a large proportion of clinical failures were reported by a small proportion of participants, demonstrating that certain couples were more prone to condom failure than others.

The PU condom eZ·on tested in the study from Bounds et al. (2002), measured 171 mm in length, 70 mm in width and 35 mm in thickness and was lubricated with a non-spermicidal silicone-based lubricant, while the second PU condom Avanti, measured 180 mm in length, 64 mm in width and 0.50 mm in thickness, and was also lubricated with a non-spermicidal silicone-based lubricant. The thinnest PU condoms (0.02 mm) identified were the Sagami Original/Protext Original (Potter & Villemeur, 2003) and Wondaleaf-On-Man (Ting et al., 2019). In general, when indicated in the identified studies, the wall of the PU condom is thinner than that of the latex condom (0.02-0.050 mm vs. 0.070-0.080 mm).

In the study from Frezieres et al. (1998), the condom breakage in the male participants with a penile circumference at the midshaft ≥ 12 cm, and penis volume ≥ 215 cm^3 were associated with increased odds of breaking an eZon condom. These findings are consistent with other studies of latex as well as non-latex condoms (Frezieres et al., 1998). Another study reported the proportion of the males reporting that the PU condom fit comfortably in terms of width was 56.8% and in terms of length was 76.7%. The comparable figures for the latex condom were 78.2% and 82.0%, respectively (Potter & Villemeur, 2003).

The Wondaleaf PU condoms have a different instruction for use, as described in the study from Ting et al. (2019). This study compared the condom failure rate, safety, and acceptability of two new synthetic adhesive male condoms, Wondaleaf-Cap (WLC) and Wondaleaf-On-Man (WLM), with a marketed latex external condom Durex-Together (DT). The participating couples used a

total of 576 condoms, with 192 condoms for each variant in this study. Clinical failure rate of WLC, WLM and DT were 1.04% (breakage=0.52%; slippage=0.52%), 0% (breakage= 0%; slippage=0%) and 0.52% (breakage=0.52%; slippage=0%) respectively. None of these differences were statistically significant (Ting et al., 2019). In conclusion, the Wondeleaf PU condoms were fundamentally different from traditional condoms in their adhesive nature, which claimed to obliviate the need for erection prior to application and reduces the risk of slippage. The preliminary findings in this study suggest that clinical failure rate of WLC and WLM were comparable to DT and did not incur serious product-related adverse events.

Published condom breakage studies typically report the percentage of failures but rarely provide any evidence on the mechanism of failure. Over a period of 7 years, broken condoms returned to the supplier SSL, Durex™ via consumer complaints were examined to determine the cause of failure. A total of n=972 returned condoms made from natural rubber and PU were examined (75.5% made from natural rubber). Visible features on those that were broken, were classified. Evidence combined from examining returns, questionnaire responses and the coital model strongly suggests a single predominant mechanism of failure which was named “blunt puncture,” where the tip of the thrusting male penis progressively stretches one part of the intact condom wall until it ultimately breaks. In this study, the blunt puncture mechanism of breakage was attributed to be responsible for more than 90% of condom breakage not attributable to misuse (White et al., 2008).

In general, the clinical failure rates (mostly breakage rate) of the PU condom are higher than that of the latex condom. However, most of the users preferred the PU condom, which provides an option for couples who have rejected conventional condoms or who cannot use latex products.

1.6.2.1.1 Prevention Pregnancy

Studies including specific pregnancy outcomes are limited. Table 1-3 shows the two studies where specific pregnancy outcomes have been estimated or measured.

Table 1-3 Pregnancy Outcomes Reported in the Literature

Study reference	Condoms Tested	Endpoints	Outcomes
Frezieres et al., 1999	Ramses Sensitol (NRL) and Avanti PU condom	Calculated 6-month pregnancy rate	4.8% (PU); 6.3% (latex)
Steiner et al., 2003	eZ·on PU condom Kimono Select (NRL)	Calculated 6-month pregnancy rate	9.0% (PU); 5.4% (latex)

Both Avanti and eZ·on PU condoms provided less pregnancy protection than the latex condom, but both the latex and PU condoms offer pregnancy protection in the range of other barrier

methods. For people with latex sensitivity or who find latex condoms unacceptable, the PU condom with its unique attributes represents one of several synthetic male condom alternatives currently available (Steiner et al., 2003).

The typical-use pregnancy rates derived from the studies suggest that the male condom is more effective than female barrier methods. For example, doubling the six-month cumulative life-table rates, adjusted for emergency contraception, yields 12-month typical-use estimates of 12.6% for the latex condom and 9.6% for the PU condom - lower than the comparable rates for female barrier methods of 20–26% (Frezieres et al., 1999).

1.6.2.1.2 Prevention of STIs including HIV Transmission

Transmission HIV

The evidence on condom effectiveness in preventing HIV transmission is supported by the WHO, CDC and UNAIDS. A position statement by these bodies stated that “male and female condoms, when used consistently and correctly, are highly effective in preventing the sexual transmission of HIV. Research among sero-discordant couples shows that consistent condom use significantly reduces the risk of HIV transmission both from men to women and women to men” (UNAIDS, 2023; WHO, 2021). According to the CDC, PU male condoms provide comparable protection against STDs/HIV to that of latex condoms (CDC, 2015, 2021c).

A study tested the effects of a brief single session behavioural skills building intervention to increase condom use among men who have sex with women. The authors examined whether introducing men to the male PU condom would enhance the effectiveness of our brief behavioural skills building intervention. Because a major barrier to men's use of latex condoms is decreased sensitivity during intercourse, the availability of a condom that is perceived to increase sensation may bolster behavioural interventions for men. To test the concept that PU condoms will increase the effectiveness of a behavioural skills intervention for men, PU male condoms were included as part of the most promising behavioural intervention available for men. The results showed the feasibility of delivering a multi-component cognitive behavioural skill building HIV risk reduction intervention in a 3 h workshop format. Although the observed effects of the intervention were small, the findings suggest that brief skills building interventions can realistically be delivered to men in community health settings. The uptake of specific preventive technologies, such as the male PU condom, can increase interest in and use of such products. There was little influence on risk reduction of introducing the PU condom into the skills building intervention. Men who used the PU condom did so in place of latex condoms, but not at a higher rate. Given that breakage and slippage rates of PU condoms may actually be higher than latex, equal use of PU condoms may not mean equal protection. Men who reported using PU condoms were more likely to report previous injection drug use and sex with men, suggesting that PU condoms may hold their greatest promise for men at highest risk for HIV infection and transmission (Kalichman & Cherry, 1999).

Transmission of other STIs

The protective value of condoms is variable. It is less protective against more prevalent infections such as HPV and HSV. The part not covered by a condom can act as a portal of entry/exit for microorganisms. The male condom offers more than 90% protection against N. gonorrhoeae, 50–90% protection against C. trachomatis as well as Treponema pallidum, and 10–50% protection against H. ducreyi (Marfatia et al., 2015).

A review summarised the results of studies investigating the protection against STI transmission while using a condom: studies showed 49–75% reduction in risk of gonorrhoea, 33% risk reduction of chlamydial infections with consistent condom use, syphilis transmission is reduced by 29% for typical use, more than 90% protection against HIV and HBV, and 10–50% protection against HSV-2 (Marfatia et al., 2015).

In the case of similar PU condoms, no studies collected sexually transmitted infection data because of the assumed rarity of these outcomes in the study population. How well pregnancy prevention serves as a proxy measure for disease prevention is not known. So far, no study comparing latex and synthetic condoms in terms of disease prevention was identified.

1.6.2.1.3 Summary of Performance Data

The literature review identified relevant studies investigating the performance of male PU condoms regarding their intended purpose as a barrier contraceptive.

The studies of relevance to contraceptive efficacy were comparative studies investigating contraceptive outcomes, mostly via surrogate endpoints of condom failure rates, of different condoms including latex and PU.

It is acknowledged that much of the protective effect of condoms relies upon consistent and correct condom use. This is influenced by sexual risk factors and behaviours of the user population and may contribute to variability in study outcomes, in addition to the problems associated with surrogate endpoints and self-reporting of condom use or failures.

Although the PU condoms have similar breakage and slippage rates, they did not perform as well as the latex condoms. In general, the nonlatex condoms were more likely to break during intercourse or withdrawal than were the latex condoms. While the eZon condom did not protect against pregnancy as well as its latex comparison condom, no differences were found in the typical-use efficacy in the comparisons between the Avanti and its latex counterpart. Substantial proportions of study participants reported preferences for the nonlatex condoms. Therefore, the nonlatex condoms appear to be an acceptable alternative for those with sensitivities, aversion, or reluctance to the use of latex condoms.

No evidence was found in the literature regarding the protection of PU condoms against STIs, however evidence for the effectiveness of other types of condoms against the transmission of

STIs is constantly evolving and may be influenced by variables such as the level of infectivity of pathogens and presence or absence of other infections; sex and sexual orientation of participants; male circumcision status; population age, characteristics, and behaviours; social and regional variables. It is generally acknowledged that condoms have a protective effect against the majority of STIs transmitted through bodily fluids, supported through epidemiological and prospective clinical data, and may offer a lesser protective effect for those transmitted via contact with infected sores, warts etc. though the data in this area is more limited. There is substantial evidence that condoms protect against HIV transmission in men and women (CDC, 2021a).

The literature suggests that, when used consistently and correctly, condoms are highly effective against unintended pregnancy and protective against the majority of STIs.

1.6.2.2 Literature Review – Safety

1.6.2.2.1 PU condoms

The safety data presented in the published literature relating to male PU condoms is discussed below. The majority of the studies identified did not include specific safety outcomes, and those that did report safety outcomes were not powered sufficiently to be able to provide meaningful safety data. However, the table below summarises the adverse events (AEs) that could be extracted. The most common reported events were genital irritation, discomfort, genital pain, and burning feeling (Table 4).

Table 1-4 Summary of the Safety Data Identified in the Studies

Study reference	Condoms tested	# of condoms used	Adverse Events (AEs)
Cook et al., 2001	eZ·on PU condom	1,283 PU condoms	One woman reported two episodes of mild genital irritation and another reported moderate genital irritation and moniliasis that were possibly related to the eZon condom. One man reported moderate genital irritation that was probably related to the eZon condom.

Study reference	Condoms tested	# of condoms used	Adverse Events (AEs)
Steiner et al., 2003	eZ·on PU condom	442 PU condoms	Number of events for Women / Man Genital pain 47 / 29 Genital pruritus 19 / 14 Genital rash 6 /3 Genital oedema 2 / 0 Vaginal discharge 2 / — Vaginal irritation 1 / — Vulvovaginitis 1 / — Intermenstrual bleeding 1 / — Menorrhagia 1 / — Postcoital bleeding 1 / — Vaginal candidiasis 1 / — Vaginal pain 0 / — Vulvovaginal dryness 0 / — Penile disorder — / 2
Frezieres et al., 1998	PU Avanti Versus a latex condom (Ramses Sensitol)	1,036 PU condoms	Male partners cited discomfort significantly less often with the PU condom than with the latex condom (15% of uses vs. 23%, p <.0001). 0001). The greater likelihood of discomfort with the latex condom was largely because men complained more often that it constricted the penis: 17% of uses of the latex condoms, compared with just 7% of uses of the PU condoms. The female participants reported discomfort slightly more often than did the men in 18% of instances in which the PU condom was used and in 23% of uses of the latex condom. Women most commonly specified irritation (8% of PU condoms and 10% of latex condoms) and burning (8% with each type of condom).
Frezieres et al., 1999	PU Avanti Versus a latex condom (Ramses Sensitol)	17,831 PU condoms	Use of PU condom was significantly (p<.0001) less likely than use of the latex condom to cause transitory discomfort to the male partner, such as irritation, itching or constriction—5.1% of 17,831 uses vs. 8.0% of 19,912 uses. Penile constriction was the most commonly reported discomfort and occurred more frequently (p<.0001) with the latex condom (6.0% of uses) than with the PU condom (2.2% of uses).

Study reference	Condoms tested	# of condoms used	Adverse Events (AEs)
			When male participants were asked how highly they would recommend their study condom, those who used the latex condom were more likely than users of the PU condom to say they would highly or somewhat highly recommend their condom to others (83% vs. 62%).
Potter & Villemeur, 2003	Sagami Original PU condoms	941 PU condoms	Burning reported: 4.4% in men 7.3% of women Prickle reported: 5.5% of men 11.7% of women Itch reported: 1.8% in men 1.0% in women None considered significant by Investigator
Farr et al., 1997	Prototype PU condom	518 PU condoms	Two adverse events, not present at baseline and possibly related to the use of the study condoms were observed. A male participant had a slightly irritated erythematous lesion on the penis. This event was resolved without treatment within two days. The second, irritation of introitus, was observed in one of the female participants during colposcopy. This event resolved without treatment within three days of the visit.
NCT04622306, 2023	Not identified PU and latex condoms	337 PU condoms A 392 PU condoms B	Mild to moderate discomfort 54.9% PU condom A 46.23% PU condom B Discomfort caused by irritation, burning sensation, itching or rash 4.45% PU condom A 4.34% PU condom B

The studies described above report adverse event data relating to PU condom use in comparison with latex condoms. For the safety outcome of genital irritation, female participants in the PU condom group reported fewer events than the latex group. One possible explanation for the higher incidence of genital symptoms among female participants in the latex group could be allergic reactions to the latex (Cook et al., 2001; Steiner et al., 2003).

Adverse reactions related to condom use reported in the literature included genital discomfort, irritation or pain, genital rash, post-coital bleeding, vaginal candidiasis, urinary tract infection and vulvovaginal dryness. However, some events may not be directly attributable to the condom themselves. Overall, reported events were mild and the number reported in the literature was low in relation to the number of participants and potential condom-use events, indicating that condom side effects are generally acceptable, particularly when weighed against the benefits of condom use.

1.6.2.2.2 NRL Condoms

NRL condoms are well established in the market. They are based on mature technology with well-established safety and performance characteristics. Literature searches were performed in April 2022 to identify published data relevant to the State of the Art in the prevention of pregnancy and transmission of STIs and publications relevant to the performance and/or safety of NRL condoms.

Adverse reactions related to condom use reported in the literature include genital discomfort, irritation or pain, genital rash, post coital bleeding, vaginal candidiasis, urinary tract infection, and vulvovaginal dryness. Some events may not be directly attributable to the condom themselves. Overall, reported events were mild and the number reported in the literature was low in relation to the number of participants and frequency of condom use, indicating that condom side effects are generally acceptable, particularly when weighed against their benefits. There are a number of reports in the literature of sensitivity to latex. In latex-sensitive individuals, up to 80% had clinical reactions to condom use. In the context of hundreds of millions of condoms used annually, the reported incidence of allergy in people not already latex-sensitised was very low. Most cases are in users with pre-existing factors such as atopic constitution, allergy to latex or cross-sensitive allergens.

The safety data presented in the published literature relating to male condoms similar to the NRL condoms is discussed below. The majority of the studies identified were not powered sufficiently to be able to provide meaningful safety data, however, Table 1-5 below summarises the adverse event statistics that could be extrapolated.

Table 1-5 Summary of Adverse Events from Similar NRL Devices Reported in the Literature

Study	NRL Condoms used	Adverse reactions (ARs) (%)	Comments
Walsh et al 2003	19,898	Genital discomfort: 3% in men (mostly constriction) 3-4% in women (mostly irritation or burning) Reported on report form or contacted staff for persistent or severe ARs.	No serious ARs reported. No men experienced genital discomfort severe enough to require treatment. Women treated themselves or sought treatment after three uses of latex condoms.
Callahan et al 2000	1,166	Condom uses resulting in 'medical event' (any genital problem that remained for <24 hrs): 7.3% for women 2.9% for men. 126 events in total.	Most common were burning, itching & genital pain. No AR thought to be product related by both men and women.
Cook et al 2001	1,382	Medical events (any genital problem that remained for <24 hrs), possibly/probably related to condom: 1.3% of women. 0.6% of men, 1.3% female, 0.6% male	No serious ARs Genital burning and genital irritation were the most commonly reported medical events.

(Cook et al., 2001) reported few adverse events in either group and none were classed as serious. Three of the adverse events reported were considered possibly or probably related to the Kimono Select condom. One woman reported genital irritation and genital rash, and another reported severe genital oedema and labial oedema. One male participant reported a mild genital rash which was considered as possibly related to the latex condom. Medical events defined as 'genital symptoms' that occurred during the use of the study condoms that were transient in nature (duration of less than one hour) included genital burning, irritation, itching, rash and

bruising and were also collated as part of this study. Genital irritation and burning were the most commonly reported medical events.

Similar safety results were also obtained from Callahan et al (2000) relating to the Aladan latex condom. In total, 126 medical events were reported for the Aladan latex condom. The percentage of condom uses in which a medical event occurred in the female partner was 7.3% and in the male partner was 2.9% for the latex condom. The most common were irritation, burning, itching and genital pain.

The number and severity of adverse events reported in the studies mentioned above are considered to be very low in relation to the number of participants and potential condom use events and therefore condoms risk benefit ratio is considered to be positive.

Much of the protective effect of condoms is determined by consistent condom use. Condom use errors including incomplete use (estimated prevalence 1.4% to 60%), incorrect application and withdrawal (prevalence 2.1% to 45.7%) and use of unsuitable lubricants (4.7% to 19.2%) can lead to condom breakage and slippage.

1.6.3 Conclusion

Summary of Safety Data

The studies described above report adverse event data relating to condom use; however, the majority were not sufficiently powered to be able to provide meaningful safety data.

Adverse reactions related to condom use reported in the literature included genital discomfort, irritation or pain, genital rash, post-coital bleeding, vaginal candidiasis, urinary tract infection and vulvovaginal dryness. However, some events may not be directly attributable to the condom themselves. Overall, reported events were mild and the number reported in the literature was low in relation to the number of participants and potential condom-use events, indicating that condom side effects are generally acceptable, particularly when weighed against the benefits of condom use. Reports of allergy to latex in condoms have been associated with risk factors such as atopic constitution, with allergy to latex or cross-sensible allergens caused by other latex products. The incidence of latex allergy in people not already latex-sensitised is considered to be very rare.

Summary of Identified Condom Risks

Adverse Events

The most common events reported in the literature are mild-to-moderate genital irritation or pain. The number and severity of adverse events reported in these studies are very low in relation to the number of participants and condom usage.

Latex Allergy

There are a small number of reports in the literature of sensitivity to latex: in latex-sensitive individuals, up to 80% had clinical reactions to condom use. In the context of hundreds of millions of condoms used annually, the reported incidence of allergy in people not already latex-sensitised was very low. Most cases are in users with pre-existing risk factors such as atopic constitution, allergy to latex or cross-sensitive allergens.

Failure of Condom and User Error

Male condoms protect against pregnancy 98% of the time when used correctly and consistently, and 80% of the time during normal use. This is one of the highest success rates after implantable and long-lasting hormonal methods (WHO 2017-accessed 2024).

Much of the protective effect of condoms is determined by consistent condom use. This is influenced by the sexual behaviours of the group that are being investigated and the population in which they circulate socially. Studies demonstrate that the overall percentage of clinical breakage and slippage of condoms in general remains low. Condom use errors including incomplete use (estimated prevalence 1.4% to 60%), incorrect application and withdrawal (prevalence 2.1% to 45.7%) and use of unsuitable lubricants (4.7% to 19.2%) can lead to condom breakage and slippage.

Overall Clinical Breakage Rate

The overall percentage of clinical breakage reported in the literature which relates to similar NRL devices is 3.5% or below, excluding the 4.7% seen when participants reported rushed application. In the majority of studies, the clinical breakage rate was 1.6% or below. The slightly higher breakage rates (3.5%) for Durex Gossamer NRL condom may be attributed to the small sample size in the study by Bounds et al. (2002). In the study by Golomok et al. (2001), breakage rates were lower (~2%) when inappropriate use was excluded. Factors that contributed to failure were identified as lack of lubricant particularly on the outside of the condom, duration of intercourse, penis length and personal characteristics of the users (Golomok 2001).

Clinical Slippage Rates of PU and NRL

Clinical (complete) comparison of slippage rates between PU and NRL condoms reported in the above are 3.5% or below, excluding the rushed application rates in the study by Crosby et al. (2015). In both cases this is representative of the data available on the breakage and slippage rates of NRL condoms. The levels of slippage found by Macaluso et al. (2000) can be attributed to the differing definition of slippage used which included incomplete slippage. The higher breakage and slippage rates seen by Golomok et al. (2001) were reduced to ~2% when incorrect use was excluded from the data.

All risks identified during literature searches are known risks in relation to condom use.

Clinical Investigation

A clinical investigation of the breakage and slippage rates of a Durex PU condom of PUD formulation KT612 compared to a standard NRL condom has been conducted by the manufacturer as discussed above and the PU condom was shown to be non-inferior to the latex condom in the combined breakage and slippage Clinical Investigation. This data is relevant to the range of Durex PU condoms of the same PUD formulation KT612.

The principles of the ISO standard for synthetic condoms were applied (ISO 23409:2011 and ASTM D6324-11(2023)) to Durex PU condoms with silicone lubricant it can be concluded that Durex PU condoms of formulation PUD KT612 with silicone lubricant can be expected to provide the intended performance in terms of prevention of STIs and pregnancy when correctly used. Based on the information provided it may be concluded that both PU and latex condoms are suitable for use as intended.

1.6.4 Summary of Previous Clinical Experience

The investigational PU condoms within the scope of the clinical investigation are yet to be marketed and as such there is no post market data available.

1.7 Benefits / Risks Assessment

This investigation has been designed to evaluate the performance rate of the two different sizes of PU male condoms when compared with the NRL condom. Participants in this investigation are healthy volunteers who would not be expected to gain any additional medical benefit from using the above devices. The findings of this investigation have potential to contribute to future advancement contraceptive methods, thereby expanding the options available for other individuals.

The investigation does not involve any procedures that pose a significant risk, however due to the nature of this investigation, there is a likelihood that couples may experience condom failure (slippage or breakage). Participants who are at risk of pregnancy or at significant (high) risk of contracting sexually transmitted infections are excluded from participating in the investigation. Minor/mild side effects related to use of condoms and lubricant may include device allergy, genital symptoms like discomfort, irritation, itching, burning, rash and redness of the genitalia. These adverse effects are anticipated to have a limited duration and resolve on their own. Participants will be instructed to contact the Investigator to report and discuss any adverse events experienced during the study. Couples who believe they are at risk of pregnancy will be assisted to access to emergency contraception and will be provided appropriate follow-up. Also, as the participants are required to reliably use effective contraception, as per the inclusion criteria, the risk of pregnancy is expected to be low. As couples will have been mutually monogamous for at least three months prior to enrolment, participants will be a low risk of STI. If a participant believes themselves to be at risk of an STI they will be referred to a health care provider and exited from the study.

Male condoms made from NRL have a long history of safety and effectiveness and their performance during use is well established; the adverse reactions associated with NRL condoms are well known and documented in the IB. This includes genital discomfort, genital burning, irritation and itching. More rarely, skin swelling, penile artery occlusion and penile vascular disorder may occur. In addition, latex allergy can cause symptoms such as irritant contact dermatitis or in more severe cases, anaphylaxis.

The adverse reactions associated with PU condoms are documented in the IB. This could include but are not limited to genital irritation, genital pain/ discomfort, genital burning, genital itching, genital rash and erythema.

Although participants known to be allergic to NRL or any other ingredient of the products used in the study are excluded from the study to minimize risks related to allergy, it cannot be ruled out with all certainty that allergic reactions to the investigational medical devices and additional lubricant may occur. The participants of the study will be informed accordingly.

Additionally, couples will also have access to sexual health information and consultation (if required) with the clinical site.

All participants will receive comprehensive instructions on the proper use of condoms through verbal and written communication. They will also be informed to promptly reach out to investigation site staff in case they experience any issues related to the investigation or encounter major medical problems. An emergency Identification Document (ID) card, containing information about participation in this investigation and usage of IP (e.g., NRL condom) and relevant contact details in case of an emergency/side effects, will be provided to the participant with the first delivery of IP. Participants will be instructed to provide this card to healthcare professionals in the event of a medical emergency.

The investigation includes safety measures expected of a condom performance study in healthy participants. Therefore, the overall benefit-risk profile for the use of the investigational products as defined in this CIP is considered as favourable.

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, ISO 29943-1:2017 Condoms - Guidance on clinical studies and applicable state, local and federal regulatory requirements including United States (US) Code of Federal Regulations (CFR) applicable to clinical medical device investigations (21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21 CFR Part 11, and 21 CFR Part 812).

1.9 COVID-19

There is no longer a COVID-19 public health emergency in effect at any of the 3 geographic locations where the investigation will be conducted.

The investigation procedures will follow state and local policy for COVID-19 infection control should a public health emergency re-emerge.

2 INVESTIGATION OBJECTIVES AND ENDPOINTS

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

ISO 29943-1 Condoms – Guidance on clinical studies has been used to guide the selection of these investigation's objectives.

Table 2-1 Investigation Objectives and Endpoints

Objectives	Endpoints
Primary Objectives:	**Primary Endpoints:**
• To evaluate the performance (total clinical failure) of PU male test condom (Test condom 1) compared with the NRL male control condom during vaginal intercourse in healthy monogamous couples.	• The total clinical failure rate (combined breakage and slippage) of PU male test condom (Test condom 1) compared to the NRL male control condom.
• To evaluate the performance (total clinical failure) of PU male test condom (Test condom 2) compared with the NRL male control condom during vaginal intercourse in healthy monogamous couples.	• The total clinical failure rate (combined breakage and slippage) of PU male test condom (Test condom 2) compared to the NRL male control condom.
Secondary Objectives:	**Secondary Endpoints:**
• To evaluate the clinical breakage and clinical slippage respectively of the PU male test condom (Test condom 1) compared with the NRL male control condom when used during vaginal intercourse in healthy monogamous couples.	• The total clinical breakage rate of the PU male test condom (Test condom 1) compared to the NRL male control condom. • The total clinical slippage rate of the PU male test condom (Test condom 1) compared to the NRL male control condom.
• To evaluate the clinical breakage and clinical slippage respectively of the PU male test condom (Test condom 2) compared with the NRL male control condom when used during vaginal intercourse in healthy monogamous couples.	• The total clinical breakage rate of the PU male test condom (Test condom 2) compared to the NRL male control condom. • The total clinical slippage rate of the PU male test condom (Test condom 2) compared to the NRL male control condom.

• To evaluate the non-clinical breakage and non-clinical slippage respectively of each PU male test condom and the NRL male control condom when used during vaginal intercourse in healthy monogamous couples.	• The total non-clinical breakage rate for each of the PU male test condoms and the NRL male control condom. • A measure of the total non-clinical slippage rate for each of the PU male test condoms and the NRL male control condom.
• To evaluate the user acceptability of the 2 PU male test condoms and the NRL male control condom.	• User acceptability, experience, and preference of each condom type will be evaluated through participant perceived questions.
• To evaluate the in-use tolerability of the 2 PU male test condoms and the NRL male control condom.	• In-use tolerability of each condom type will be evaluated through participant perceived questions.
Safety Objective:	**Safety Endpoints:**
• To assess the safety of the 2 PU male test condoms and the NRL male control condom.	• Overall proportion of participants with Adverse Events / Adverse Device Effects (AEs/ADEs), i.e., the occurrence of one or more AEs/ADEs per participant.
Exploratory Objectives:	**Exploratory Endpoints:**

• To evaluate total clinical failure, clinical breakage, clinical slippage, non-clinical breakage, and non-clinical slippage rates in users according to whether additional lubricant was used.	• For each condom type:
	  ○ The total clinical failure rate by whether additional lubricant was used or not used.
	  ○ The total clinical breakage rate by whether lubricant was used or not used.
	  ○ The total clinical slippage rate by whether additional lubricant was used or not used.
	  ○ The total non-clinical breakage rate by whether additional lubricant was used or not used.
	  ○ The total non-clinical slippage rate by whether additional lubricant was used or not used.
	• The total clinical failure rate (combined breakage and slippage) of PU male test

	condom (Test condom 2) compared to the NRL male control condom for participants in Penis Size Category 1 (mid shaft lower limit greater than or equal to 128mm).
• To evaluate sexual pleasure during the use of 2 PU male test condoms and NRL male control condoms via EMSEX pleasure scale and Quality of Sexual Experience (QSE) Scale.	• Score of each item, the condom pleasure subscale score, and the overall scale score in EMSEX pleasure scale from male participants for each condom type. • Score of each item and scale score in QSE Scale from male and female participants for each condom type.
• To evaluate correlations among size, fit, and performance of the 2 PU male test condoms and NRL male control condom, including factors of erect penile size (length and girth), user condom size preference (previous of and during the investigation), size of each condom type used in the investigation (PU male test and NRL male control condom), comfort/fit with condoms, and condom performance (total clinical failure, clinical breakage, clinical slippage, nonclinical breakage, and nonclinical slippage rates).	• Erectile penile length and girth measured by a given penis measuring tool. • Evaluation through participant perceived questionnaire of users' previous experience and preference of condom size. • Evaluation through participant perceived questionnaire of users' preference of comfort and fit of the condoms used in this investigation.

2.1 Success Criteria

ISO 29943-1:2017 Condoms – Guidance on clinical studies for the primary endpoint requires an upper one-sided 95% confidence limit for total clinical failure rate (combined breakage and slippage) of the Polyurethane (PU) male test condoms minus Natural Rubber Latex (NRL) male control condom to be less than 2.5%. To control the overall type 1 error rate at ≤5%, non-inferiority will be concluded if the upper one-sided 97.5% confidence limit is 2.5%, if the upper one-sided 97.5% CI is above 2.5% then the investigation will have failed to demonstrate non-inferiority. If only one comparison is non-inferior, then the investigation will be considered to be a partial success.

3 INVESTIGATION, DESIGN AND RATIONALE FOR DESIGN

3.1 Investigation Design

This is a randomised, data analyst-masked, 3-way cross-over pivotal clinical investigation. This investigation is designed to compare the performance (clinical failure rate) of two different sized

Polyurethane (PU) male test condoms and the commercialized NRL male control condom based on the guidance set out in ISO 29943-1 Condoms – Guidance on clinical studies.

The clinical investigation population and investigational sites should be heterogeneous and represent males with different penis sizes therefore, this investigation will include participants recruited from 3 different geographic regions in the United States of America (USA) and the investigation population will include males with different penis sizes (please refer to Section 4.1 Investigation Population for the details).

This investigation will be conducted via a Decentralised Clinical Trial (DCT) approach from a single investigational site. Participants will not be required to attend the clinical investigation site physically for routine study appointments. All visits will be held virtually via teleconference/video call, phone calls or curbside visits except for emergency situations or adverse event assessments which may require a participant to be seen and assessed at an emergency hospital or at a private clinic. There will be 3 remote visits via video/phone call or teleconference: video consent and instruction (Visit 0), screening visit (Visit 1), and exit visit (Visit 6). Four curbside visits (Visit 2-Visit 5) will be arranged for delivery and collection of the study supplies by Site staff. Further details regarding the curbside visits are given in Section 6.12. Additional phone contacts will be conducted prior to each curbside visit as needed.

Following the Visit 0 consent and instruction and Visit 1 screening visits for each partner, eligible couples will attend the Visit 2 curbside visit (commencing Assessment Period 1), where they will receive their first set of a test condoms according to the randomisation schedule. Within Assessment Period 1, couples will be asked to use the condoms provided for 5 separate acts of vaginal intercourse (in total 7 condoms, 2 of them are spare condoms, will be provided for each assessment period). After each assessment period, Site staff will collect unused IP from the couple and provide them with the next condom type according to the randomisation schedule, with the final collection taking place after Assessment Period 3. Participants will be informed not to use the condom if it feels too tight or too loose and causes significant pain or discomfort during use. In such cases, they will be required to contact the site for further instructions. The designated site staff will then schedule the next curbside visit to collect the unused condoms and provide the next set of test condoms according to the randomisation schedule. Additional phone contacts will be conducted prior to each curbside visit as needed.

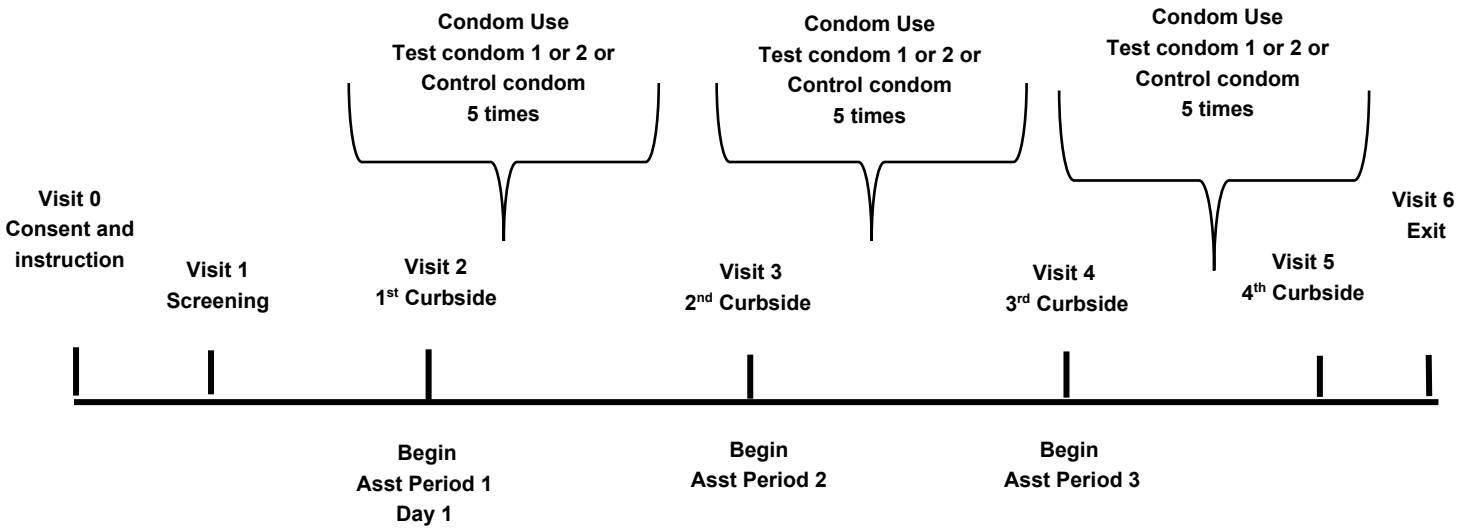
On completion of each assessment period, couples will be required to attend their next curbside visit (please see Section 6.12) to return their unused condoms and collect their second or third condom type (according to the randomisation schedule).

The exit visit will occur within 7 (+7) days after the completion of the final assessment period.

The duration of the clinical investigation is anticipated to be approximately 19 weeks (from screening to follow-up).

The investigation design is outlined in the schematic below (Figure 3.1).

Figure 3.1 Investigation Design Schematic



Visit 0: Consent- Screening: within 7 (+7)* days prior to Day 1.

Visit 1: Screening: within 7 (+7)* days prior to Day 1.

Visit 2: 1st Curbside.

Assessment (Asst) Period 1: Day 1. Same day as the 1st curbside visit.

Visit 3: 2nd Curbside.

Assessment (Asst) Period 2: Within 7 (+7)* days after assessment period 1.

Visit 4: 3rd Curbside.

Assessment (Asst) Period 3: Within 7 (+7)* days after assessment period 2.

Visit 5: 4th Curbside: within 7 (+7)* days after assessment period 3.

Visit 6: Exit phone visit within 7 (+7)* days after assessment period 3.

*The period prior to each Visit is 7(+7) days. Only instances where this period extends beyond 7(+14) days shall be recorded as a deviation.

3.2 Rationale for Investigation Design

The two Polyurethane (PU) male test condoms will be compared with a commercially available Natural Rubber Latex (NRL) male control condom for functional performance (breakage and slippage), acceptability and in-use tolerability through the questionnaires. This investigation

design has been developed in accordance with ISO 29943-1:2017 Condoms- Guidance on clinical studies.

Per relevant ISO 29943-1:2017 requirement, the control condom should be made from NRL and selected from a standard commercial design that is representative of condoms typically found in the market, justified with respect to study population of market and condom design and quality. Therefore, Durex NRL male condom (57± 2 mm width and 50 ± 2 µm thickness) is selected as the control condom. It is commercialized in the USA, as one of the current thinnest Durex NRL condom variants.

Both test condom types and the NRL control condom will be debranded and provided to the participants as randomised to use within a 5-week period. Following use of the first condom type, the participants will then receive the second condom type, followed by the third condom type at their subsequent visits. The investigation will be executed by implementing the decentralised approach, where the participants are not required to attend the site physically for investigation assessments, this allows participants to be enrolled from a wider geographic pool. Increasing diversity within the study population and reducing barriers, allowing more convenient study participation. Please refer to Section 7 for the details of each visit.

To be successful, both Polyurethane (PU) test condoms will demonstrate non-inferiority to the Natural Rubber Latex (NRL) control condom with a non-inferiority margin of 2.5%. If only one comparison is non-inferior, then the investigation will be considered a partial success. Please see Section 2 for a full presentation of the objectives of this investigation.

3.3 Determination of Sample Size

Data from a previously conducted study, CIP number 1003201, was used to determine the sample size used within this clinical investigation. This is a proposed 3x3 crossover clinical investigation with two test (T_1, T_2) products and a control (C). If we first, consider this as two individual trials (i) T_1 vs C and (ii) T_2 vs C and setting the Non-Inferiority (NI) margin at 2.5% or 0.025. Then if we let each Confidence Interval (CI) be a one tailed 95% the type I error overall would be something between 5 and 10%, if we wish to control the overall type 1 error rate at ≤5% then we need to use 2 one-tailed 2.5% limits for a one-sided CI, i.e., a one-sided 97.5% CI. If the power to achieve NI for each of (i) and (ii) is set to 90% then the power to achieve both could be as small as 81% (0.90^2). Thus if we wish this to be ≥90% then each NI test should be planned for 0.95, so that $0.95^2 \approx 0.90$(90%) power (to see NI of both Tests vs C).

To retain the overall alpha level of the 3x3 we require the CI's on which the 2 NI tests are based to be 1-sided 97.5% CI's and to retain the power at 90% to achieve both T_i's to be NI to C, we need to power each test at 95%. The numbers (N's) previously calculated for a 2x2 protocol (e.g., Clearglass 1003201, one T vs C) for equal treatment group failure rates of 2%, 3% and 4% were N=86, 128 and 169 couples. Running the same calculations with the above detailed revisions on α and 1-β we obtain Total N of couples = 131, 194 and 256 for failure rates of 2%,

3% and 4% respectively. A total of 300 couples would allow a dropout rate of approximately 15% for the study to realise 256 completers, which would provide 90% power of demonstrating NI of both Tests vs Control over the range of failure rates (2-4%) foreseen in this type of investigation.

According to ISO 29943-1:2017 the investigation should enrol a sufficient number of couples, so a minimum of 200 couples complete the clinical investigation. Because of attrition, it is prudent to enrol extra participants to ensure sufficient numbers at end of clinical investigation. The clinical investigation should ensure a minimum 1000 uses of each condom type.

Considering the calculation of sample size from a previous study, the ISO guidance and potential dropouts, the aim is to enrol 300 couples across the 3 investigation locations to achieve 256 completers ensuring a minimum of 1280 uses of each condom type (which is more than 1000 uses per condom type as per the ISO guidance) for a 90% power of demonstrating NI of both Tests vs Control respectively for a 4% failure rate foreseen in this type of investigation.

4 SELECTION AND WITHDRAWAL OF PARTICIPANTS

4.1 Investigation Population

The aim is to enrol 300 healthy monogamous heterosexual couples remotely from three different geographic locations by one investigational site. Recruitment locations were selected based on population diversity with respect to race and socio-economic groups. This will be enabled through the use of electronic systems (e.g., eConsent, ePRO) and delivery of investigational product to the participant by the site, removing the requirement for participants to travel to site. Participants will be trained and supported in the use of these systems throughout the investigation by site staff.

All couples will test all 3 products across the 3 periods, therefore there will be no stratification in this investigation. The males in each couple (one male and one female participant in each couple) will represent potentially different penis sizes. Based on data derived from the penis measuring tool, which participants' will record in the Penis Measurement Form, the couples will be classified into Penis Size Category 1 (which is a group of participants whose mid-shaft penis girth size is ≥128mm) and Penis Size Category 2 (which is a group of participants whose mid-shaft penis girth size is <128mm). For details on how participants are classified into either Penis Size Category 1 or 2, please refer to Appendix 2 - Assignment of Penis Size Category.

The target proportion for each Penis Size category is approximately 150 couples, with a flexibility of ± 30 couples (approximately 120 couples in one Penis Size category, with 180 couples in the other Penis Size category) however, recruitment will continue until 300 couples have been enrolled.

Participants' eligibility will be checked against the inclusion and exclusion criteria. Participants who are deemed ineligible at any stage prior to randomisation will be regarded as screening

failures. Any participant who becomes ineligible after the point of randomisation will be withdrawn from the investigation according to the withdrawal criteria and will not be replaced (Please refer to the Section 4.5 for details of discontinuation / withdrawal and replacement of participants).

4.2 Inclusion Criteria

Only participants (both partners of participating couples) to whom all of the following conditions apply will be included:

1. Both partners participating must provide written informed consent.
2. Couples must include a male and female within a heterosexual couple and be between 18 – 60 years of age inclusive.
3. Both partners must be willing to respond to questions about their reproductive and contraceptive history and use of condoms during interviews and respond to self-administered questionnaires as per instructions.
4. Both partners must agree to answer the questions in the condom use questionnaires and two scales as soon as possible and within 2 (+6) hours following each coital act.
5. Both partners must be generally healthy and in a mutually monogamous heterosexual relationship - current relationship ≥ 3 months.
6. All couples must be averaging one act of intercourse weekly, agree to have penile-vaginal intercourse with a frequency sufficient to meet CIP requirements (a minimum of 5 coital acts over 5 weeks per assessment period).
7. The female partner must also use an established (as agreed by the Investigator) other highly effective form of non-barrier contraception, unless post-menopausal (confirmed menopausal prior to screening, amenorrhea for at least 12 months after cessation of exogenous hormone treatment) in which case no second form of contraception is required. Highly effective non-barrier contraception includes oral contraceptive (oestrogen and progestogen or progestogen-only hormonal contraception associated with inhibition of ovulation), intra-uterine device (IUD) or intra-uterine system (IUS), hormonal implant, injectables, patch and or sterilization of at least one partner (i.e., bilateral tubal ligation, vasectomy deemed medically successful).
8. Both partners must be able to understand instructions for correct use of condoms.
9. Both partners must have an adequate level of literacy to understand and to be able to answer the questionnaires.
10. Both partners must agree to use only the investigational condoms during the time of participation.
11. Participants must agree to use the penis measuring kit provided to measure the erect penis at investigation start.

12. Both partners must agree not to use drugs or non-investigational devices that can affect sexual performance.
13. Both partners must have no known sexually transmitted infections including Human Immunodeficiency Virus (HIV) / acquired immune deficiency syndrome (AIDS) (medical history via self-report)(uncomplicated Herpes simplex virus (HSV) and positive Human papillomavirus (HPV) which are asymptomatic may be included in the investigation in the opinion of the Investigator).
14. Both partners must agree to use only lubricant(s) provided for the duration of investigation.
15. Both partners must agree not to wear any genital piercing jewellery for the duration of the clinical investigation.
16. Both partners must have no past medical history of any health condition (self-reported) that, in the opinion of the Investigator, would be considered clinically relevant.
17. Couples must have a compatible electronic device with internet access which they are willing to upload questionnaire data to the web-based platform throughout the investigation.
18. Both partners will be available for follow-up.

4.3 Exclusion Criteria

Couples to whom any of the following conditions apply to either one or other of the partners must be excluded:

1. Either partner is or becomes aware of an allergy or sensitivity to the ingredients of any of the products, including the test or control condoms or any lubrication products provided.
2. Either partner has been receiving daily treatment for their pre-existing skin condition (for example, severe eczema/psoriasis) within the three months prior to the screening for this study.
3. Female partner that is pregnant or desires to become so while participating in investigation, (females of childbearing potential must have a negative pregnancy test as part of screening).
4. Any couple undergoing any form of fertility treatment such as in-vitro fertilisation.
5. Either partner needs to use condoms for sexually transmitted infection (STI) protection (e.g., discordance for Human Immunodeficiency Virus (HIV) or herpes).
6. Either partner has previous or planned genital surgery that in the opinion of the Investigator would consider the participant unsuitable to participate in the clinical investigation (e.g., laser for abnormal smear).
7. Either partner are commercial sex workers.
8. Either partner are itinerant persons who will be unable to complete the clinical investigation (e.g., migrant farm workers).
9. Couples that in the opinion of the Investigator, would be unable to complete the investigation.
10. Male partners that have known erectile or ejaculatory dysfunction in the past month.
11. Either partner requires to use/ is using medication or preparations that are applied topically to the genitalia area or intravaginally, other than that supplied for the investigation.

12. A female partner that has been diagnosed with or treated for vaginal complaints (including vaginal dryness) in the previous 3 months which, in the opinion of the Investigator, deems the partner unsuitable for the investigation.
13. Either partner uses any medication which in the Investigator's opinion may interfere with the use of condoms.
14. A male partner with abnormal penile anatomy or genital lesion (e.g., balanoposthitis) that would, in the opinion of the Investigator, affect the ability to keep the condom in place during intercourse.
15. Either partner is suffering from any health conditions (self-reported) or any condition which could, in the opinion of the Investigator, affect the outcome of the investigation or affect their safety if they participate.
16. Either partner have participated in a clinical trial in the previous month which could, in the opinion of the Investigator, affect the outcome of the investigation.
17. Either partner is an employee of the investigational Sponsor or affiliated with the clinical research centre (i.e., enrolment of the Investigator, his/ her family members, employees and other dependent persons).
18. Either partner has a recent history of drug/alcohol abuse within the previous 12 months.
19. Either partner has an inability to follow the procedures of the investigation, (e.g., due to language problems, psychological disorders, health conditions such as dementia).
20. Either partner is unable, in the opinion of the Investigator, to fully comply with the investigation requirements.

4.4 Investigation Restrictions

If the Investigator or designee becomes aware of an investigation restriction being contravened by a participant, this will be recorded as a deviation. An assessment will be made and recorded by the Investigator to determine whether this affects participant's safety or data integrity, and whether the participant may continue participating in the investigation.

4.4.1 Dietary and Lifestyle Restrictions

Dietary and Lifestyle restrictions for participants are listed in Table 4-1 below:

Table 4-1 Dietary and Lifestyle Restrictions

Restriction	From	To
Use of any prescription medication, preparations or non-prescription medication, which the Principal Investigator considers may interfere with the safe use of investigational products.	Screening visit	Last investigation condom use
Use of any drugs or non-study devices that can affect sexual performance.	Screening visit	Last investigation condom use

4.4.2 General Restrictions

General investigation restrictions for participants are listed in Table 4-2 below:

Table 4-2 General Restrictions

Restriction	From	To
Sexual intercourse without established reliable contraceptive method	Screening visit	Exit visit
Sexual activity including masturbation	Within at least 24 hours prior to each condom use. However, only instances occurring within 22 hours will be recorded as a protocol deviation.	
Use of more than one investigation condom for a single coital act.		
Enrolment into another clinical investigation/ study.	1 month prior to screening visit	Exit visit
A change of partner	3 months prior to screening visit	Exit visit
Use of any other type of condoms or lubricant except for the one provided by site staff	Screening visit	Exit visit

In the event either partner does not comply with general restrictions as mentioned in Table 4-2, an assessment will be made and recorded by the Investigator to determine whether this affects their safety or data integrity, and whether the couple may continue participating in the investigation. All non-compliance will be recorded as a deviation.

4.5 Discontinuation / Withdrawal and Replacement of Participants

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

- AEs/ADEs that in the judgement of the Investigator may cause severe or permanent harm (significant clinical deterioration is a Serious Adverse Event/ Serious Adverse Device Effect (SAE/ SADE)).
- Violation of the CIP, which in the judgement of the Investigator affects either partner's safety or data integrity, wellbeing.
- In the Investigator's judgment, it is in the participant's best interest (this includes inadequate device performance).
- Either partner declines further investigation participation.

- If applicable, randomisation code is broken.

The primary reason for withdrawal of the couple will be documented in the electronic Case Report Form (eCRF).

If the couple chooses to prematurely stop the investigation at least 2 documented attempts should be made to contact the participants for exit assessments which will include assessments as described for the exit visit (Section 7.8).

In the event of any persistent medical issues potentially related to study condom use (e.g., penile rash with condom use) considered to be clinically significant, participants will be followed up with appropriate medical management. Referral or collaborative care will be arranged if considered necessary.

The aim is to enrol 300 couples in the investigation. Couples who withdraw from the investigation before receiving any investigational product (IP) will be replaced (i.e., prior to randomisation). Couples who withdraw after they have been randomised to IP will not be replaced.

5 INVESTIGATION TREATMENT

5.1 Medical Device

Those investigational products (IPs) to be used for this investigation are listed in Table 5-1 below:

Table 5-1 The Condom Key Dimensions

	Polyurethane (PU) Male Test Condom 1	**Polyurethane (PU) Male Test Condom 2**	**Natural rubber latex (NRL) Male Control Condom**
Reference (TDS Code) for condom	PIBOM 3243906 (PUCON10, PULUB4)	PIBOM 3247902 (PUCON9, PULUB5)	GPA50008601 (CON73, LUB7)
Reference (TDS Code) for additional lubricant used	011053 (silicone NM1 350): 3225236 (Silicone oil 100 EP), 1:1	011053 (silicone NM1 350): 3225236 (Silicone oil 100 EP), 1:1	FRM10032456
Thickness (Micron µm)	30 ± 5 µm	35 ± 5 µm	50 ± 2 µm
Length (mm)	185 ± 10 mm	185 ± 10 mm	190 ± 10 mm
Width (mm)	57 ± 2 mm	63 ± 2 mm	57± 2 mm

Shape	Straight wall shape	Straight wall shape	Straight wall shape
Colour	Transparent	Transparent	Transparent
Materials	Polyurethane, Silicone oil	Polyurethane, Silicone oil	Natural rubber latex, Silicone oil with mask odour (Zeus)
Known Allergens	No ingredients known to cause allergy	No ingredients known to cause allergy	Latex
Primary pack	Butter dish	Butter dish	Foiled condoms
Lubricant type used	Silicone (350EP:100EP, 1:1)	Silicone (350EP:100EP, 1:1)	Silicone with Zeus (Silicone 350 EP)
Lubricant level	Min. 700 mg	Min. 800 mg	480 ± 50 mg
Batch (Lot) No	Batch number(s) will be recorded in the the Investigational Materials Supplies Unit (IMSU) files.	Batch number(s) will be recorded in the IMSU files.	Batch number(s) will be recorded in the IMSU files.
US 510(k) Clearance	Investigational products – not 510(k) cleared	Investigational products – not 510(k) cleared	510k no. K200672
Manufacturer	Lanzhou Keshi Xixili Healthcare Technologies Co.,Ltd Ketian Waterborne Science and Technology Industrial Park, No. 3949 Kunlunshan Road, Lanzhou New Area, Lanzhou, Gansu, P.R. China	Lanzhou Keshi Xixili Healthcare Technologies Co.,Ltd Ketian Waterborne Science and Technology Industrial Park, No. 3949 Kunlunshan Road, Lanzhou New Area, Lanzhou, Gansu, P.R. China	Qingdao London Durex Co., Ltd, No. 1-13, Shangma Part Aodong Road, Hightech Industrial Development Zone, Qingdao City, Shandong Province, P.R. China

Test condoms and the control condoms will be manufactured and packed (primary pack) in accordance with the Good Manufacturing Practice (GMP) standards by the manufacturers as listed above. The test and control condoms will be shipped to the Investigational Materials Supplies Unit (IMSU), Reckitt, Dansom Lane, Hull, HU8 7DS for assembly.

The test and control condoms will be assembled to GMP standards by the IMSU, Reckitt, Dansom Lane, Hull, HU8 7DS and certified by Reckitt Research and Development Quality. The IPs will be shipped from IMSU to the investigational sites.

5.2 Non-Investigational Products

Lubricant is applied to the test condoms and control condom before packaging. However, couples may desire additional lubricant, as standard, KY True Feel Lube (TDS Code: CPBOM 3019801) will be supplied to all couples. This product is a non-investigational product (non-IP), and a silicone oil-based lubricant, which is compatible with both PU test condoms and NRL control condoms.

The non-IP will be packed (primary pack) to GMP standards by Reckitt.

The non-IP (additional lubricant) will be debranded and assembled by IMSU to GMP standards and certified by Reckitt Research and Development Quality. The non-IP (additional lubricant) will be shipped by IMSU to the investigational sites. Further details will be documented in an IP Handing Manual.

5.3 Concomitant Therapies

Any treatment considered necessary for either partner's welfare or change of the concomitant medication must be reviewed by the Investigator. Please refer to Section 4.4 investigation restriction section for restricted medications.

Concomitant medication e.g., investigation concomitant therapies, 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 (if applicable) for which the concomitant therapy was administered in the (e)CRF.

5.4 Treatment Compliance

Each couple will be required to use each condom type 5 times over a maximum period of 5 weeks (assessment period). The assessment period may be extended at the discretion of the Investigator in discussion with the participants, recorded as a protocol deviation.

No more than one investigational condom should be used in each coital act. Participants will be requested to refrain from sexual activity, including masturbation, for 24 hours prior to each condom use, however only instances occurring within 22 hours will be recorded as a protocol deviation.

Treatment non-compliance would be using each condom type less than 5 times without any reason (participant is advised to not use the condom if it feels too tight or loose).

Treatment compliance will be monitored by Site personnel via participant completion of the condom use questionnaires, the end of condom use period questionnaire, the EMSEX and QSE scales and the accountability of returned unused IP. Couples will be reminded of the need to remain compliant for the entirety of the clinical investigation.

Couples who do not use condoms as instructed and/or complete study questionnaires or scales will be questioned by site staff and withdrawn from the clinical investigation where appropriate.

Couples will receive electronic reminders such as phone notifications to encourage the frequency of use of the condoms during each assessment period. They will also receive notifications reminding them to complete the Condom Use Questionnaires, the EMSEX and QSE scales.

Lubricant is added to both test condoms and control condoms during manufacture. All couples will receive a supply of additional lubricant as standard and re-supply upon request. The use of lubricant will be captured in the Condom Use Questionnaire following each coital act.

5.5 Packaging and Labelling and Supply / Resupply

One kit per couple will be assembled by the Investigational Materials Supplies Unit (IMSU). Each kit (outer box) will contain three inner cartons: one carton containing 7 of the PU male test condom product, second carton containing 7 of the other PU male test condom and third carton containing 7 of the NRL male control condoms.

Each condom will be individually wrapped. In addition to the kits, the investigational site will be supplied with a bulk supply of debranded lubricant (non-IP) to be provided to couples that routinely use/desire to use lubricant during coitus.

The kits, inner cartons, individual condoms, and lubricant will be labelled in accordance with 21 CFR Part 812 and any other applicable legislation. The IPs and non-IPs will be labelled with text in English language. The label or participant information shall describe all relevant contraindications, adverse effects, warnings, and precautions.

Test products, control products and non-IP lubricant labels will include, but not limited to:

- Investigational Material Supply Unit (IMSU) order and label reference number
- Product ID

- Quantity
- Batch/Lot Number
- Expiry Date
- Reckitt CIP number
- Sponsor Address and Telephone Number
- Storage Instructions
- CAUTION—Investigational device. Limited by Federal (or United States) law to investigational use
- Emergency Contact Number
- Instruction for use: use as directed by provided instructions for use leaflet
- “Keep out of the reach and sight of children”
- Kit number
- Caution: This Product May Contain Natural Rubber Latex Which May Cause Allergic Reactions (this item is applicable for the condom products only)

All the product assembly and labelling will be performed per the IMSU Processes and SOPs.

See Section 6.3 for details of administration of investigational and non-investigational products.

5.6 Storage Conditions

The Investigator or designated individual will keep all of the investigation supplies in a secure location, accessible only to those individuals authorised by the Investigator to dispense the IPs and non-IPs.

IP kits should be kept protected from direct sunlight in a dry, cool and well-ventilated area at a temperature not above 30°C. Non-IPs, the lubricants, should be stored in a cool dry place, protected from direct sunlight. Further details will be documented in an IP Handing Manual.

Temperatures must be monitored, recorded weekly, and readings available for review by the monitor with a record included in the Investigator Site File. The temperature log will be reviewed by the clinical investigation monitor at each monitoring visit.

There is no requirement for the temperature conditions to be monitored during the journey to the curbside visits, however, product must be dispensed to participants (or returned to storage in the event of a cancelled visit) on the same day that they are removed from storage location.

If the IP storage temperature falls outside the specified range (i.e., above 30°C), the Sponsor should be notified immediately, and appropriate action will be agreed and documented.

5.7 Masking

The clinical investigation is designed to be a data analyst-masked investigation where the data analyst, who will perform the data analysis (both CRO and Sponsor staff involved in analysing

the data) will not know which condom type couples have been randomised to use in each assessment period.

All investigational products will be debranded. Each condom will be contained within an individual packet, a butter dish for PU condoms or aluminium foil for NRL, which has been tested for stability (data held at Sponsor). Each set of 7 condom types will then be put in an identical box and tamper sealed. All the condom types will be debranded in the same manner and identical boxes will be used for the PU male test condoms and NRL male control condom.

Due to the composition of Test and Control male condom materials, an inherent difference can be observed between their appearance and softness. The PU male condoms are clear, transparent and stiffer whereas the NRL male condom is transparent and softer. As a result of the inherent appearance of the condom packets and the condoms, participants may notice a difference between condom types when provided in each assessment period.

There will be no specific masking procedure for the site.

5.8 Unblinding Procedures

The unblinding means the same as unmasking. The randomisation code will only be accessed for a couple who has experienced a Serious Adverse Event (SAE) / Serious Adverse Device Effect (SADE) that requires knowledge of which condom was used so that the SAE/SADE can be treated appropriately.

The participant may use the emergency Identification Document (ID) card to identify potential allergens in the event of emergency to provide to treating physicians. Physicians may use the emergency ID card contact details to obtain more information from unmasked personnel. Unmasked personnel may identify the IP via the randomisation schedule.

The PI may withdraw the couple based on an evaluation of the participant's ability to complete the investigation and their safety to continue. If the couple is withdrawn from the clinical investigation, site staff will document the details of the event in the eCRF and promptly inform the Sponsor.

5.9 Accountability of Investigational and Non-Investigational Products

The Investigator will keep all of the investigation supplies in a secure storage location, accessible to those individuals authorised by the Investigator to dispense the condoms.

Accurate device accountability at the investigational site is an important and key element of the Sponsor's ability and obligation to trace all IP (used and unused) during the investigation. Consequently, the Investigator or delegate is obligated to maintain device accountability in the Investigator Site File (ISF).

The designated site staff will maintain an inventory using kit numbers as a reference. This will include the description and quantity of kits received during the course of the clinical 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 reviewed by the clinical investigation monitor during monitoring visits.

It is anticipated that IP will be supplied in a kit and non-IP supplied in bulk from a single batch number. The Investigator or delegate will maintain a full record of IP and non-IP accountability.

An IP and non-IP Dispensing Log must be kept current and will contain the following minimum information:

- Kit number dispensed.
- The date(s) kit(s) was/were dispensed.
- The IP quantity dispensed for each participant and participant ID.
- Batch/Lot number for IP.
- The date(s) IP dispensed.
- Batch/Lot number for non-IP (additional lubricant).
- The date(s) non-IP was dispensed.
- The non-IP quantity dispensed for each participant and participant ID.

The inventory must be available for review by representatives from the Sponsor during the investigation.

Full device accountability for the IP and non-IP will be maintained from release by the IMSU at Reckitt, through storage. Custody of the used product within the site facility and culminating in the return of unused product to the Sponsor.

5.10 Return and Destruction of Investigational and Non-investigational Products

At the end of the investigation, the Investigator or designee(s) will conduct a full IP and non-IP supply reconciliation and will record the results of the reconciliation. Following review of the reconciliation, any unused investigational and non-investigational products will be returned by the Investigator or designee(s) to IMSU for destruction (6 months after the finalisation of CIR) according to applicable Sponsor Standard Operating Procedures (SOP's).

6 INVESTIGATION PROCEDURES

6.1 Informed Consent

The purpose and requirements of the investigation will be explained before prospective participants are presented with an informed consent. Participant will also be advised that more detailed information about sexual activity will be collected than is typical of most family planning visits. Participants will be given an opportunity to ask questions about the investigation and/or the content of the informed consent. Participants will be informed that their partners must also

agree to participate in the investigation in order for them to join. If both participants of the couple agree to participate, they will each sign the informed consent form separately. The informed consent form will include each of the basic and additional elements of informed consent described in 21 CFR Part 50.25. All participants will be required to provide written informed consent before they are enrolled in the investigation. All participants will receive a copy of their signed informed consent form. In this investigation, electronic informed consent form (eICF) will be used. For details about the ICF, please see Section 7.3.

Should participants need to be made aware of new information that arises during the investigation, an updated ICF will be provided, and the above process repeated to confirm that participants wish to continue in the investigation. For participants who have completed the investigation, the Investigator will decide if this new information needs to be provided to them.

The electronically signed ICF for each participant will be verified by the monitor and kept in the electronic investigational site files (eISF).

6.2 Randomisation

This is a data analyst-masked clinical investigation. The data analysts from the CRO and Sponsor performing and reviewing the statistical analysis will not be aware of which condom participants are randomized to use in each assessment period until the analysis is completed and the unmasking process has been followed. The assigned unmasked statistician on this study from the vendor will generate a dummy randomisation schedule using SAS version 9.4 or higher and the assigned masked statistician from the sponsor will review the dummy schedule. After approval from the Sponsor, the unmasked CRO statistician will generate the true randomisation schedule. Table 6-1 provides of an example of a randomised block of 6.

The CRO will hold the master randomisation schedule and will provide the master randomisation schedule to the Sponsor and Investigator for the purpose of dispensing. Upon randomisation into the clinical investigation, the participants will be assigned a unique patient randomisation number from the master randomisation schedule by an Interactive Response Technology (IRT) system.

Table 6-1 Example of Block Design for Location One

Participant Number	Randomisation Number	Assessment Period 1	Assessment Period 2	Assessment Period 3
1	100 001	Condom 2	Condom 1	Condom 3
2	100 002	Condom 3	Condom 2	Condom 1
3	100 003	Condom 1	Condom 3	Condom 2
4	100 004	Condom 3	Condom 2	Condom 1
5	100 005	Condom 2	Condom 1	Condom 3
6	100 006	Condom 1	Condom 3	Condom 2

Details on the production of the randomisation schedule will be captured in the Data Management Plan (DMP).

If there are any changes to the proposed CIP randomisation schedule described in this CIP these will either be documented in the final DMP or in a CIP amendment prior to the first participant first visit with the rationale and impact of the changes addressed.

6.3 Administration of Investigational and Non-Investigational Products

Participants will be trained in the use and handling of the investigational condoms (verbally, visually and in a written format). Couples will not be given the full condom kit at their first curbside visit. Following randomisation, the couple will receive one of the condom cartons (inner box) from their kit per randomisation schedule. This will contain 7 condoms and at least 5 condoms should be used during the first assessment period (maximum of 5 weeks). Each condom must be used for penile-vaginal intercourse only. Participants will be instructed to use only one investigational condom for a single coital act. In the situation of condom breakage or condom slippage, a couple may continue to have intercourse without the investigational condom only if they believe they are not at risk of an STI or pregnancy.

At the end of the first assessment period, participants should return all unused condoms at the second curbside visit where they will then be given the second condom carton (containing 7 condoms) from their kit to be used during the second assessment period maximum 5 weeks. This is to be repeated in the third assessment period for the final condom type.

The assessment period may be extended at the discretion of the Investigator in discussion with the participants, recorded as a protocol deviation.

Each coital act must be at least 24 hours apart. Participants will be instructed to refrain from any sexual activity including masturbation within at least 24 hours prior to each condom use, however only instances occurring within 22 hours will be recorded as a protocol deviation. For each condom use, as soon as possible and within 2 (+6) hours the couple will complete a

Condom Use Questionnaire, an EMSEX pleasure scale (only male partner) and QSE Scale (both partners) (Refer to Section 6.9 Questionnaire and Scale for the details)

For non-compliance, refer to Section 5.4 'Treatment Compliance'.

During the clinical investigation, participants are permitted to use the investigation provided lubricant as they wish. Any use of additional lubricant will be recorded in the Condom Use Questionnaire.

6.4 Demographics

Baseline characteristics and demographic information will be recorded. This will include but not be limited to:

- Biological sex
- Child-bearing potential (female participants)
- Year of birth
- Race
- Education
- Employment
- Annual income
- Marital status
- Condom experience

6.5 Medical History and Prior Therapies

Current and historical medical diseases, conditions or surgeries, will be collected from each partner separately and privately. All current therapies such as prescription or non-prescription drugs, including vitamins, herbal and dietary supplements, and non-pharmacological treatments such as physiotherapy from the 2 weeks prior to screening and through the end of the investigation will also be recorded. The backup method of contraception to be used during the clinical investigation will also be confirmed and recorded.

6.6 Physical Examination

A symptom targeted physical examination for a reported AE will be performed by a medically qualified delegate at the Investigator discretion.

6.7 Pregnancy Test

Pregnancy testing (females of childbearing potential only, as determined by the PI) is required at the beginning of the investigation and at the end of the last assessment period.

An over-the-counter pregnancy test kit (urine based) will be used for the pregnancy test. The pregnancy test kits will be sourced from a reputable business or pharmacy by the principal Investigator or designated person. Participants will be provided easy to use tests that display

the result clearly in word format to prevent misinterpretation of test results (e.g., misidentification of faint lines in the result window).

Principal Investigator or designated site staff will provide a pregnancy test kit to the participants. Female participants will follow the instructions to perform the test. Then the participant will enter the result into the web-based platform as soon as they performed the test. Participants will receive instructions on how to record the data into the web-based platform. The web-based system will transfer this data into the eCRF. Principal Investigator or designated site staff will check the result to confirm the eligibility. Participants do not need to return the used and unused pregnancy test kit.

6.8 Penis Measurement

Male participants will be asked to use a penis measuring tool, which allows for a consistent means of measuring the erect penis length and circumference, per the participant user guide document and training by the delegated site staff.

This penis measuring tool has been developed by the Sponsor, and the Sponsor will provide it along with the participant user guide to investigation sites. The Investigator user guide document details how the participant will be trained to use the tool. Site staff who are responsible for instructing participants will be provided training on the correct use of penis measuring tool.

Male participants will be provided with the penis measuring tool and the participant user guide document during the first Curbside- Visit 2. Male participants will use the tool at home. The measurement should be done after the penis is fully erected but before intercourse starts. Participants will be asked to complete the penis measurement during Assessment Period 1. However, the measurement may be also done in later assessment periods if the tool was lost in assessment period 1 or for any other reason that caused a delayed measurement. Participants should enter their penis size data into the web-based platform (at the earliest time after the measurement has been taken (no later than 12 hours after). Participants will receive instructions on how to record the data into the web-based platform.

The participant user guide and Investigator user guide documents will be submitted to IRB for their review.

The Penis Measurement data will be used to classify participants into Penis Size Categories 1 and 2. See Appendix 2 for the measurement conversion calculation, Penis Size category assignment and information on how the enrolment into each Penis Size category will be monitored.

6.9 Questionnaires and Scales

During the clinical investigation, 3 participant perceived questionnaires and 2 validated scales as described below will be utilised.

6.9.1 Study Entry Questionnaire

Each partner will be asked to independently answer a Study Entry Questionnaire (some questions will only apply to one partner and for some questions the male partner may consult with their partner) as part of being screened for eligibility. The questionnaire will collect (including, but not limited to): demographics, condom experience, sexual relationship and activity. Some of the questions within this questionnaire will assist in identifying participant's condom preference and grouping these participants based on condom sizes into Groups A and B (see Appendix 1) which will be used for the exploratory analysis (see Section 9.5.3).

6.9.2 Condom Use Questionnaire

Each couple will be asked to complete a Condom Use Questionnaire for every condom used as soon as possible and within 2 (+6) hours after each coital act (per condom type). The questionnaire will collect the following event information (including, but not limited to) for each condom used: type of intercourse, condom breakage information (prior to, during and after intercourse), condom slippage information (prior to, during and after intercourse) and lubricant usage.

6.9.3 End of Condom Use Period Questionnaire

Upon completion of each assessment period (at least one condom used during the assessment period), each partner will be required to complete an End of Condom Use Period Questionnaire no later than their next visit. The questionnaire will collect the following information (including, but not limited to): experience with condom use, acceptability, preference and tolerability.

An assessment period for a type of condom is considered as completed for a couple when any one of the below is met:

- 5 weeks have passed since a participant of the couple received assessment period IP. The assessment period may be extended at the discretion of the Investigator in discussion with the participants, recorded as a protocol deviation.
- when a minimum of 5 condoms in the carton have been used during vaginal intercourse by the couple and the couple has confirmed that they have completed the assessment period,
- when all the 7 condoms in the carton are used,
- after initial use of an assessment period condom, a participant or Investigator decides that the couple should not, or are unable to use the remaining condoms in the carton during vaginal intercourse because for example, an allergy or other AE, donning issues including the condoms being too tight or too loose, loss of contact, etc. Participants are informed that all condoms in a single carton are identical to each other.

The end of assessment period is defined as the point at which the couple has completed the Condom Use Questionnaire following use of their fifth, or final condom (in cases where condom

use is ceased due to the reasons above), within the 5-week assessment period. The assessment period may be extended at the discretion of the Investigator in discussion with the participants. Only instances where an assessment period is greater than 7 weeks will be recorded as a protocol deviation.

6.9.4 Event-Level, Male Sexual Pleasure Scale

Male participants will be asked to complete an Event-Level, Male Sexual Pleasure Scale (EMSEXpleasure) for each coital act using investigational condoms as soon as possible and within 2 (+6) hours after the coital act. EMSEXpleasure scale is an 11-item scale which assesses sexual pleasure at the event level (Aaron J et al, 2018). For each item, the range spans from 0 (zero) to 100 (one hundred).

6.9.5 Quality of Sexual Experience Scale

Both partners will be asked to independently complete a Quality of Sexual Experience (QSE) scale for each coital act using investigational condoms as soon as possible and within 2 (+6) hours after the coital act. QSE scale is a 7-item scale used to measure the event-level quality of a sexual experience (Stephanie at al, 2013). Each item is rated on the scale ranging from 1 to 7. The nearer the point is to 1, the more the participant agrees with the statement on the left; the nearer the point is to 7, the more the participant agrees with the statement on the right side.

6.9.6 Completeness Check of Questionnaires and Scales

Principle Investigator or designated person will review the database to ensure the completeness of the questionnaires/scales (Study Entry Questionnaires, Condom Use Questionnaires, End of Condom Use Period Questionnaires and EMSEX and QSE scales) and ensure the data entry quality.

6.10 Assessment of Used Condoms

Clinical and Non-Clinical Breakage*

A clinical breakage is defined as a breakage or tearing of the condom during intercourse or withdrawal from the vagina. This might not be noticed until after inspection of the condom following intercourse.

Any breakages that do not meet the definition of clinical breakage are considered “non-clinical breakage” (e.g., tearing the condom when opening the package).

Clinical and Non-Clinical Slippage*

A clinical slippage is defined as a condom slipping off completely during intercourse or during withdrawal from the vagina.

Slippage that occurs due to the user failing to hold onto the condom at the base of the penis during withdrawal and/ or because the user delayed withdrawal after sex and is no longer erect, are to be record as “non-clinical slippage, these events are considered user failures”. Therefore, these user failures will not be counted as clinical slippage events. If a condom slips off primarily because of a breakage, this will also not count as a slippage event.

* Definitions have been taken from BS ISO 29943-1:2017 Condoms – Guidance on clinical studies.

Couples will be instructed to examine the condom carefully after the penis is withdrawn but before the condom is removed from the penis. Any breakages or slippages (as defined above) should be noted in the condom use questionnaire which will be reviewed by site staff after completion of the couple’s assessment period. Used condoms will be dispose by the couples as instructed.

6.11 Adverse Events

The observation period for an individual participant will start after the participant has signed the consent form and will finish at the couple’s phone exit visit. All AEs that arise during the observation period will be recorded and an assessment of the AEs will be performed as per Section 8.2 by a medically qualified Investigator or a medically qualified Sub-Investigator. If a participant has an AE that is still ongoing at the last visit, an attempt will be made by delegated site staff to follow this up as per Section 8.4.

An untoward medical occurrence that happens after the participant’s eligibility confirmation but before receiving study condoms should be reported as an AE, including those associated with investigation procedures.

6.12 Curbside Visits

Curbside visits will be held in this investigation. These visits will allow the delegated site staff to meet participant(s) at a suitable prearranged location (e.g., clinic parking lot, library) which ensures safety for both the participants and delegated site staff during the exchange of study materials e.g., IP, Non-IP (additional lubricant), pregnancy test kit, penis measuring kit.

Curbside visits will be arranged by the delegated site staff via video conference/phone calls/text messages prior to each visit.

If the participants are able to drive to the meeting site, they will remain in their vehicles while the delegated site staff are carrying out necessary procedures outside. Alternatively, the visit can be conducted at another predetermined location that affords sufficient privacy.

At the first curbside visit, both partners must be present and provide official government-issued photo identification to re-verify their identity before they can receive any study materials. The delegated site staff must also show their company card ID. Identification verification will be

performed at each visit. It is planned that each couple will attend four curbside visits, but the total number of curbside visits may vary as additional visits may be required to address various situations such as the need for additional lubricant or replacement of a condom kit or penis measuring kit. Following the first curbside visit, it is not mandatory to have partners attend future visits.

There is no requirement for the temperature conditions to be monitored during the journey to the curbside visits, however, product must be dispensed to participants (or returned to storage in the event of a cancelled visit) on the same day that they are removed from storage.

A record of the date, quantity, curbside location and site staff transporting study supplies is recorded on an IP Tracking Sheet. All investigation materials are transported by private vehicle in the main cab (not in the trunk) and kept out of direct sunlight. The IP and non-IP is not left unattended in the car and no non-delegated staff are allowed in the car.

7 INVESTIGATION PROCEDURES BY VISIT

7.1 Investigation Flow Chart / Table of Investigation Procedures and Assessments

Table 7-1 Schedule of Assessments

Visit	Visit 0 - video	Visit 1 video/phone	Visit 2 1st curbside	Visit 3, 4, 5 2nd, 3rd, 4th curbsides	Visit 6 - phone
Period	Consent and Instructions	Screening	Assessment Period 1	Assessment Periods 2 &3	Exit
Day / Procedures*	Within 7 (+7) days prior to Day 1	Within 7 (+7) days prior to Day 1	Day 1	Within 7 (+7) days after each assessment period	Within 7 days (+7) days after 3rd assessment period
Identification verification	X	X	X	X	X
Informed consent	X				
Inclusion/ exclusion[1]		X	X	X	
Demographics		X			
Medical history & concurrent conditions		X			
Concomitant medication/products		X	X	X	X
Pregnancy test[2] (female participants only)		X			X
Study entry questionnaire completion		X			
Investigator confirmation of participants eligibility		X			
Penis measurement[3] (male partners only)			X	X	
Penis measuring training[4]	X				
Physical examination[5]		X	X	X	X
Randomisation[6]			X[5]		
Provide/ dispense investigational product[7]			X	X	
Collect/return investigational product[8]				X	
Provide access & login details & training to the web-based plarform[9]	X				
Review completed Condom Use Questionnaires and 2 scales[10]			X	X	
End of Condom Use Period Questionnaire Completion			X	X	
Completion of EMSEX pleasure and QSE Scale			X	X	
Adverse events & adverse device effects	X[11]	X	X	X	X

* All procedures above apply to both male and female partners in all couples unless otherwise stated.

1. Eligibility will be confirmed at Visit 1 as part of the screening visit. Continued eligibility will be confirmed at each assessment period.
2. Female participant of childbearing potential must have reported a negative pregnancy prior to Visit 2.
3. Male partners will be asked to measure the erect penis length and circumference using a penis measuring kit at home. A penis measuring kit will be provided to male partners at Visit 2 to be used during assessment period 1. Penis measuring may also be performed during assessment periods 2 or 3 if required such as due to the loss of the kit.
4. Penis measuring kit training will be given at Visit 0 and it may also repeated if required.
5. Physical examination for a reported AE will be performed by a medically qualified delegate at the Investigator discretion.
6. Randomisation to be performed at Visit 2.
7. Couples will be provided their assigned condoms in accordance with the randomisation schedule at Visits 2, 3 and 4. Additional lubricant will also be supplied at Visit 2 as standard and at Visits 3 or 4 upon request.
8. Any unused investigational and non-investigational products will be returned at curbside on Visits 3, 4 and 5.
9. Both partners will be provided access to the web-based platform to complete questionnaires and scales and training on how to use the platform and how to enter the data.
10. The questionnaire and scales will be reviewed by clinical site staff for completeness at the end of the 1st, 2nd, and 3rd assessment periods.
11. AE collection will be started after the participant has signed the consent form. Excludes ADEs.

7.2 Recruitment

Participants will be recruited by the site centrally in three distinct geographic locations. The delegated staff member will provide a brief summary of the investigation and address inquiries from individuals who have expressed interest in participating in the investigation through various recruitment strategies such as contacting individuals who previously participated in an EAH study, and using platforms like Craigslist, social media, and Google Callers will be directed to the recruitment website where they can obtain additional IRB approved information about investigation participation and request contact from a delegated study representative.

A delegated site personnel will conduct a preliminary screening using a questionnaire approved by the IRB to assess the potential investigation eligibility of the caller and their partner.

The questionnaire will be prepared based on the final CIP by the Investigator or delegated person with Sponsor oversight. If the caller and their partner pass the phone pre-screening and remain interested in study participation, the delegated investigation representative will schedule them for a remote consent and instruction Visit (Visit 0) dedicated to obtaining their formal consent.

An electronic IRB approved Participant Information Leaflet (PIL) will be emailed to the caller. An electronic version of the IRB approved Informed Consent Form (ICF) will also be sent to any caller who would like to review the ICF prior to Visit 0.

7.3 Visit 0- Consent and Instruction Visit

The informed consent process will be conducted remotely via videoconference with both partners present using one video camera. Both partners will show a valid, official government-

issued photo identification for verification. Delegated site staff will show EAH issued photo identification. Couples will receive information about the investigation and each partner will receive an IRB approved electronic informed consent form (eICF) in case they haven't received it prior to this Visit (Visit 0), oral and written information describing the nature and duration of the investigation and the investigation procedures. Sufficient time will be given to each partner to decide whether to participate or not. Site staff will explain to the couple the nature of the investigation, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort they may experience. The couple will be informed that participation in the investigation is voluntary and that he / she may withdraw from the investigation at any time and that withdrawal of consent will not affect his / her relationship with Principal Investigator or site staff. The Investigator or delegated person will provide the participants with any additional information or clarification as required.

Both partners should understand the information provided in the eICF before signing and dating the eICF. After this explanation, if the couple agrees to take part, they will be required to sign and date the electronic informed consent form using their finger or a stylus on their personal electronic device. The Investigator or qualified delegated person obtaining consent will also sign and date the eICF. Each partner needs to sign the eICF individually. Each participant will receive a copy of the signed informed consent and written information.

After signing the informed consent, each couple will be issued a screening number. Both partners will view a video which will demonstrate the correct way to don and remove condoms and how to use the penis measuring tool. Couples will be instructed that the penis should be withdrawn completely soon after ejaculation, while holding the condom firmly in place at the base of the erect penis (ISO 23409:2011 clause 6.2.3.3.d). Couples will be encouraged to ask questions to demonstrate their comprehension of the instructional videos and delegated site staff will help to clarify any unclear directions. The delegated site staff will also instruct the couple on the use of the penis measuring tool per the requirements listed in Section 6.8. The participants will be provided refresher training if required.

Both partners will be provided with login details to access the study entry questionnaire (SEQ), condom use questionnaires, the EMSEX pleasure, the QSE scales and the End of Condom Use Period Questionnaire. The couple will be trained by delegated site staff on how to enter their information into the web-based platform.

Each partner will be instructed to complete a Study Entry Questionnaire (separately and privately) on a web-based platform that elicits demographic information, relationship and sexual activity, and condom experience before Visit 1 or at the Visit 1 if required such as if participant have questions and desire to consult the site staff during the Visit 1.

The couple will be instructed to complete a condom use questionnaire together for each condom used, an EMSEX pleasure scale by the male participant and QSE scale separately by each partner for each condom as soon as possible and within 2 (+6) hours after each coital act.

Couples will also be instructed to examine the condom carefully when removing the condom from the penis, for breakages. All breakages and slippages are to be recorded on a Condom Use Questionnaire.

7.4 Visit 1: Screening Phone Visit

After informed consent has been obtained at Visit 0, each partner will separately and privately attend a remote phone/video Screening Visit (Visit 1).

Site staff will collect a brief medical history and concomitant medications or products for each partner. A physical examination may be arranged if the Investigator deems it is required (refer to Section 6.6). All clinical assessments and test results will be entered into each partner's eCRF. If Study Entry Questionnaire (SEQ) has not been completed before Visit 1, each partner separately and privately will complete the SEQ.

Site staff will instruct the female partner on how and when to perform the over-the-counter home pregnancy test and how and when to enter the result into the eCRF. For details for the pregnancy test, see Section 6.7. The female partner will be sent the home pregnancy test via mail.

Staff will complete a comprehensive screening checklist to establish the couple's eligibility. If both partners meet all inclusion and exclusion criteria, the couple will be scheduled for their first curbside visit (additional phone contacts will be conducted prior to each curbside visit as needed to clarify data).

7.5 Visit 2: First Curbside and Assessment Period 1

Following confirmation that the female partner has entered a negative pregnancy test result into the web-based platform, couples will be assigned a randomisation number and randomised to the order they will use the three condom types via the Interactive Response Technology (IRT) system.

At their first curbside (Visit 2), both partners must provide official government-issued photo identification to re-verify their identity before they can receive any study materials. The delegated site staff must also show their company card ID. Couples will be given a carton containing their first set of 5 condoms along with 2 spare condoms, with the second and third carton boxes remaining in the kit at in Site's IP storage location. All couples will receive a bottle of additional lubricant for use during intercourse. The couple will be provided with a penis measuring kit and instructions to use at home and record the measurement of their erect penis on the web-based platform. For details for the penis measurement, see Section 6.8.

One of the partners will be required to attend the second curbside (Visit 3) after using their first set of 5 investigational condoms. They will be reminded to dispose all used condoms and return all unused condoms at the second curbside (Visit 3).

The end of assessment period is defined as the point at which the couples have completed the Condom Use Questionnaire following use of their 5th, or final condom (in cases where condom use is ceased due to the condoms being unsuitable for the participant), within the assessment period. Please see Section 6.9.3 for details of “end of assessment period” definition.

Participants who require additional lubricant will be provided with additional non-IP lubricant at the second and/or third curbsides (Visit 3 and/or Visit 4).

All assessments conducted during Assessment Period 1 are detailed in Section 6 and summarised in Table 7-1. All clinical assessments and test results will be entered into the partner’s eCRF.

7.6 Visits 3 and 4: Second and Third Curbsides and Assessment Periods 2 and 3

The second and third curbsides (Visit 3 and Visit 4) will be conducted once a couple has completed the previous Assessment Period as defined in Section 6.9.3.

In advance of these Visits, delegated site staff will have examined the Condom Use Questionnaires, End of Condom Use Period Questionnaire, EMSEX pleasure and QSE scales for completeness, quality of data entry, whether it was completed within the timeframe required by the CIP and, if necessary, further training on the clinical investigation requirements will be given.

In addition, completion of the End of Condom Use Period Questionnaires by each partner will be verified. Over the phone, AEs, concomitant medications and products will be recorded and updated for each partner. Procedures and assessments performed during Visit 3 and Visit 4 will be the same as those performed during Visit 2/Assessment Period 1, except for randomisation and penis measuring kit delivery related activities which will be performed during Visit 2/Assessment Period 1 only.

If a couple fails to remain eligible for the clinical investigation, they will be withdrawn.

Following confirmation of continued eligibility, participants will be provided with the condom type from the kit to be used during Assessment Periods 2 and 3. Additional supply of additional lubricant will also be provided if required.

Couples will be required to return all unused condoms of the first and second condom type from Assessment Periods 1 and 2 at the second and third curbsides (Visit 3 and Visit 4), respectively.

All assessments conducted during Assessment Period 2 and 3 are detailed in Section 6 and summarised in Table 7-1.

7.7 Visit 5: Fourth Curbside

Delegated site staff will have examined the Condom Use Questionnaires and EMSEX pleasure and QSE scales and End of Condom Use Period Questionnaire for completeness prior to the fourth curbside. The delegated site staff will collect all unused condoms and unused additional lubricant(s) and provide a pregnancy test kit at Visit 5. All assessments conducted during Visit 5 are detailed in Section 6 and summarised in Table 7-1.

7.8 Visit 6: Exit Visit

Exit Visit (Visit 6) via phone will be conducted within 7 (+ 7) days after the completion of the third Assessment Period and Visit 5, or in the event of a couple's withdrawal from the clinical investigation. AE and concomitant medication information will be collected. In advance of the visit Female participants will be requested to take a urine pregnancy test at home and provide the results as soon as possible after they have performed the test, as detailed in Section 6.7.

7.9 Unscheduled Visits and Lost to Follow Up

If unscheduled visits occur, the Investigator or delegated person must record the following in the couple's eCRF:

- Type of visit e.g., phone or video call, curbside.
- Reason for unscheduled visit.
- Any AEs/ADEs that either partner has experienced since their last visit.
- Concomitant medication changes.
- Withdrawal (if deemed appropriate).
- Any actions, process completed during the visit.

For additional required unscheduled visits/curbsides please see Section 6.12.

Unscheduled visits should not alter the timing of the routine clinical investigation schedule. For all enrolled couples who do not attend a scheduled visit or fail to respond to site staff's attempts to reschedule, the research team will continue efforts to contact both partners until either the investigation concludes or one or both partners withdraw their consent. In case phone calls and emails are unsuccessful in re-establishing contact, site staff will send an exit package via a traceable delivery service to each partner, providing instructions for them to reach out within weeks of receiving the letter. The package will include a traceable, pre-paid return envelope for any unused investigational or non-investigational products. Furthermore, site staff will attempt contacting any backup contacts listed for the couple. If there is no response from both partners by the end of the investigation period, they would be categorized as lost to follow-up.

8 SAFETY REPORTING

The assessment and reporting of AEs in the investigation are in compliance with the guidelines on medical devices, MEDDEV 2.7/3 revision 3, May 2015 and FDA regulations (Code of Federal Regulations-CFR Title 21 Part 812).

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 participants, users or other persons whether or not related to the investigational medical device.

This includes events related to the investigational device or the comparator and to the procedures involved. For users or other persons this is restricted to events related to the investigational medical devices.

Adverse Device Effect

An Adverse Device Effect (ADE) is an AE related to the use of an 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

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequacy in the information supplied by the manufacturer.

Serious Adverse Event

A Serious Adverse Event (SAE) is an AE that:

a. Led to death, injury or permanent impairment to a body structure or a body function.

b. Led to a serious deterioration in health of the participant, that either resulted in:

- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- in-patient hospitalization or prolongation of existing hospitalisation, or
- in medical or surgical intervention to prevent life threatening illness

c. Led to foetal distress, foetal death or a congenital abnormality 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 an SAE.

Unanticipated Serious Adverse Device Effect

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

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

Unanticipated Adverse Device Effect

An Unanticipated Adverse Device Effect (for FDA) is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

8.2 Assessment of Adverse Events

All AEs that arise after the participant has given informed consent will be recorded in the participant's source documents and eCRF. AEs can be reported spontaneously by the participant 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. Participants 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 AE a causality assessment of the event to the medical device must be performed. The relationship to the medical device must be determined by the Investigator (if medically qualified) or by a medically qualified Sub-Investigator.

Relationship	Description
Not related	Relationship to the device 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. ▪ the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible. ▪ the discontinuation of medical 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 event. ▪ the event involves a body-site or an organ not expected to be affected by the device or procedure. ▪ the serious 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. ▪ harms to the participant are not clearly due to use error. 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 event.

Possibly related	The relationship with the use of the investigational device 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 where 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 seems relevant and / or the event cannot be reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The serious event is associated with the investigational device 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 event follows a known response pattern to the medical device (if the response pattern is previously known). ▪ the discontinuation of medical 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 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 participant 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 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 participant may experience slight discomfort.
Moderate	The event is sufficiently discomforting to interfere with everyday activities.
Severe	The event prevents normal everyday activities; the participant may experience intolerable discomfort or pain.

Expectedness for each AE will be determined based on the information in Section 3.1.1, 3.2.2, 3.2.3, 4, and 5 of the Investigator's Brochure (IB).

Coding of AEs and medical history will be done using Medical Dictionary for Regulatory Activities (MedDRA) V26.1 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 Global Vigilance Group (GVG) by email: gvg@rb.com 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 +44 (0)1482 326151 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 and Device Deficiency forms must be provided via email. 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 Institutional Review Board (IRB)of all SAE / SADE / USADEs and reportable Device Deficiencies occurring in the investigation as soon as possible and within 10 days as per Sponsor instructions as described in the Safety Management Plan.

The Investigator should not break the randomisation code except when it is necessary in order to ensure the participant receives appropriate medical care.

SAE / SADE / USADEs, Device Deficiencies and non-serious AE / ADEs 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 and IRBs as required by regulations. If the event requires expedited reporting, GVG will take actions as per the investigation specific Safety Management Plan.

An annual safety report will be submitted to the IRB once a year via the Investigator. 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 participant making additional visits to the site.

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

The end of the clinical investigation is defined as the last visit (phone exit visit) of the last participant. in the clinical investigation. Participants who experience the onset of an AE after the final visit will not be followed up.

All SAE/ SADE/ USADEs and all AE/ ADE that cause premature withdrawal of the participant from the clinical 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 requirement for follow-up. This may involve the participant making additional visits to the site.

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

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 CRF 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 participant 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 both in a female participant or the female partner of a male participant 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.

If the female participant reports that she is concerned that she is at risk of pregnancy she will be assisted in obtaining emergency contraception and the couple will be discontinued from the investigation as they no longer meet investigation eligibility requirements.

If the female partner reports a positive pregnancy test, the couple will be immediately withdrawn from the clinical investigation and the Sponsor must be promptly notified of the event. Any pregnancy reported during the investigation or within 30 days after discontinuation of the medical device administration 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 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. Follow-up will also be required for pregnancies in female partners of male participant.

Three documented follow up attempts should be made to follow up with the participant.

9 STATISTICAL CONSIDERATIONS

The statistical group at the CRO will be responsible for statistical activities including randomisation and analysis with the Sponsor oversight.

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) that describes the full details of the analyses to be conducted will be written and signed prior to first participant first visit.

Summary statistics for continuous variables will typically include the number of participants, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables,

summary statistics will typically include the number and percentage of participants in each category. All data will be presented in listings.

Baseline values are defined as the last measurements taken prior to randomisation.

9.1 Statistical Analysis Plan

Details of statistical methods and analysis will be documented in the SAP. The SAP will be approved prior to first participant first visit (FPFV).

9.1.1 Changes to the Original Statistical Analysis Plan

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

9.2 Interim Analysis

No formal interim analysis is planned, however data will be analysed after a defined number of observations to identify any patterns of missingness. A data review plan containing details of this analysis will be developed, and a data report will document findings. Further details regarding this are in Section 9.7.

9.3 Analysis Datasets

The analysis populations will be as followed:

- The Full Analysis Set (FAS) population will include all randomised participants who use at least one of either of the PU male test condoms or NRL male control condom. The FAS will be used for the analysis of all efficacy endpoints. For the FAS, participants will be analysed according to their randomised treatment.

- The safety population will include all randomised participants who use at least one of the either of the PU male test condoms or NRL male control condom. The safety population will be used for all baseline summaries and summary of safety data. For the safety population, participants will be analysed according to treatment received.

- The Per Protocol (PP) population will consist of all participants in the FAS who do not deviate from the protocol in such a way as to impact the evaluation of the primary endpoint. All decisions on exclusions from the PP population will be made prior to database lock. For the PP population, participants will be analysed according to treatment received. If more than 10% of the FAS population incur a protocol deviation, then the PP population will be used for sensitivity analysis of the primary endpoints.

Since this is a non-inferiority clinical investigation, both the FAS and PP populations will form the primary analysis (if a PP population is required). The FAS population will be used to confirm

the primary objectives and the test of superiority. Protocol violations will be further defined in the SAP and will be identified prior to the unmasking of the randomisation codes.

9.4 Participant Disposition and Characteristics

The number of participants screened, randomised, completing, and withdrawing, along with reasons for withdrawal, will be tabulated. The number of participants in each analysis population will be reported. Demographic and baseline characteristics (including but not limited to age, gender and race) will be summarised using descriptive statistics. No formal statistical analysis will be performed.

9.5 Statistical Analyses

All statistical analyses will be performed using SAS® version 9.4 or higher. For all endpoints, in the event that the assumptions underlying the parametric approach are violated, alternative non-parametric methods will be used.

9.5.1 Primary Endpoint(s)

There are two primary endpoints of the investigation:

- The total clinical failure rate of the PU male test condom 1 compared to the NRL male control condom.
- The total clinical failure rate of the PU male test condom 2 compared to the NRL male control condom.

The clinical failure rate is calculated as the number of condoms with at least 1 acute failure event (e.g., clinical slippage or clinical breakage) divided by the number of condoms used during intercourse. The clinical failure rate will be reported as a percentage.

A condom that experiences multiple clinical failure events only counts as a single clinical failure.

Both two test PU male condoms must be non-inferior to NRL male control condom with a non-inferiority margin of 2.5%. If only one comparison is non-inferior then the investigation will be considered to be a partial success.

9.5.1.1 Primary Analysis

The primary null hypothesis is that the total clinical failure rate for each PU male test condom is inferior to the NRL male control condom where the non-inferiority margin (δ) is 2.5%. The alternative hypothesis is that the total clinical failure rate for each PU male test condom is non-inferior to the NRL male control condom. These can be written as:

H0: PU male test condom 1 total clinical failure rate – NRL male control condom total clinical failure rate ≥ 2.5%

Vs

HA: PU male test condom 1 total clinical failure rate – NRL male control condom total clinical failure rate < 2.5%

and

H0: PU male test condom 2 total clinical failure rate – NRL male control condom total clinical failure rate ≥ 2.5%

Vs

HA: PU male test condom 2 total clinical failure rate – NRL male control condom total clinical failure rate < 2.5%

For the primary endpoint, each condom usage during vaginal intercourse will be considered either a clinical success or a clinical failure. It will be considered a clinical failure if either the condom breaks or tears during intercourse or withdrawal from the vagina, or the condom slips off completely during intercourse or during withdrawal from the vagina. Since the outcomes of each condom use by a particular couple are expected to be more alike than the outcomes of condom use by another couple, this within-couple correlation should be accounted for in the analysis. A generalised estimating equations (GEE) model with an identity link function and independent working correlation structure will be used to analyse the total clinical failure rate. Covariates will include condom type (i.e. treatment), location and investigational period. Interactions between condom type and centre will be investigated, and if found to be non-significant at the 10% level of significance ($p>0.1$), the interaction term will be dropped from the final model. If an interaction is detected, then further analyses will be performed to understand the nature of the interaction and the results will also be presented separately for each investigational location.

From the GEE model, the difference in the proportion of condoms experiencing failure in the test and control condoms will be presented together with an upper one-sided 97.5% confidence limit. If the upper limit is less than 2.5%, this will provide sufficient evidence that the test condom is non-inferior to the NRL control condom with respect to clinical failure.

If non-inferiority is achieved, a test of superiority can then be performed. As per ISO 29943-1:2017 Condom – Guidance on clinical studies, in order to declare superiority, the upper limit of the one-sided 97.5% confidence interval will need to be <0%.

In the event of a low failure rate in the reference group, the accuracy of the GEE models deteriorates, in that the Type 1 error is inflated above 0.05. ISO 29943-1:2017 Condom – Guidance on clinical studies recommends rates of no lower than 0.5% in the reference group as the threshold. If the reference group failure rate is <0.5% then an exploratory analysis will be

performed at a more stringent significance level, such as an alpha level of 0.025, to help provide assurance in the investigation conclusions.

Further to the primary analysis, interactions between condom type and investigational location will be investigated, and if found to be non-significant at the 10% level of significance ($p>0.1$), the interaction term will be dropped from the final model. If the interaction term in the model is significant, then further analyses will be performed to understand the nature of the interaction and the results will also be presented separately for each investigational location.

9.5.2 Secondary Endpoint(s)

The following are secondary endpoints of the investigation:

- The total clinical breakage rate of the PU male test condom 1 compared to the NRL male control condom.
- The total clinical slippage rate of the PU male test male condom 1 compared to the NRL male control condom.
- The total clinical breakage rate of the PU male test condom 2 compared to the NRL male control condom.
- The total clinical slippage rate of the PU male test condom 2 compared to the NRL male control condom.
- The total non-clinical breakage rate of each of the PU male test condoms and the NRL male control condom.
- The total non-clinical slippage rate of each of the PU male test condoms and the NRL male control condom.
- User acceptability, experience, and preference of each condom type, evaluated through participant perceived questionnaires.
- In-use tolerability of each condom type, evaluated through participant perceived questionnaire.
- The total clinical breakage rate is determined from the number of condoms broken or torn during vaginal intercourse or withdrawal from vagina.
- User acceptability, experience, and preference of each condom type, evaluated through participant perceived questionnaires.
- In-use tolerability of each condom type, evaluated through participant perceived questionnaire.

The total clinical breakage rate is determined from the number of condoms broken or torn during vaginal intercourse or withdrawal from vagina divided by the number of condoms

during intercourse, reported as a percentage.

The total clinical slippage rate is determined from the number of condoms that slipped completely off the penis during intercourse or withdrawal from vagina, divided by the number of condoms used during vaginal intercourse, reported as a percentage.

The total non-clinical slippage rate is determined from the number of observations where the user fails to hold onto the condom at the base of the penis during withdrawal and/ or because the user delayed withdrawal after sex.

The total non-clinical breakage rate is determined from the number of condoms that tear during handling.

9.5.2.1 Secondary Endpoint Analyses

Clinical slippage and clinical breakage rates will be analysed using the same GEE methodology as described for the primary endpoints. Both of these secondary endpoints will be compared between each polyurethane test and the control NRL condom as a non-inferiority hypothesis test. In accordance with ISO 29943-1:2017 Condoms – Guidance on clinical studies, the non-inferiority margin will be slightly smaller than that specified for the total failure rate and will be set at 2.0%.

Hence the hypotheses to be tested for these secondary endpoints are:

Breakage:

H0: PU male test condom 1 total clinical breakage rate – NRL male condom total clinical breakage rate ≥ 2.0%

Vs

HA: PU male test condom 1 total clinical breakage rate – NRL male control condom total clinical breakage rate < 2.0%

and

H0: PU male test condom 2 total clinical breakage rate – NRL male control condom total clinical breakage rate ≥ 2.0%

Vs

HA: PU male test condom 2 total clinical breakage rate – NRL male control condom total clinical breakage rate < 2.0%

Slippage:

H0: PU male test condom 1 total clinical slippage rate – NRL male control condom total clinical slippage rate ≥ 2.0%

Vs

HA: PU male test condom 1 total clinical slippage rate – NRL male control condom total clinical slippage rate < 2.0%

and

H0: PU male test condom 2 total clinical slippage rate – NRL male control condom total clinical slippage rate ≥ 2.0%

Vs

HA: PU male test condom 2 total clinical slippage rate – NRL male control condom total clinical slippage rate < 2.0%

The difference in the proportion of test and reference condoms experiencing (1) clinical breakage or (2) clinical slippage will be presented together with an upper one-sided 95% confidence interval. If the upper limit is less than 2.0%, this will provide sufficient evidence that the test condom is non-inferior to the control condom with respect to clinical breakage or slippage.

For each of the above secondary endpoints, if non-inferiority is achieved, a test of superiority can then be performed. In order to declare superiority, the upper limit of the one-sided 97.5% confidence interval will need to be <0%.

Non-clinical slippage and non-clinical breakage rates will be summarised as the proportion of the two polyurethane test and control NRL condoms experiencing each outcome, using descriptive statistics only.

User acceptability, experience, preference and in-use tolerability of each condom type will be summarised using descriptive statistics and/ or frequency tables.

9.5.3 Exploratory Endpoints

The following are exploratory endpoints of the investigation:

- For each of the two PU male test condoms and the NRL male control condom:
    - The total clinical failure rate by whether additional lubricant was used.
    - The total clinical breakage rate by whether additional lubricant was used.
    - The total clinical slippage rate by whether additional lubricant was used.
    - The total non-clinical breakage rate by whether additional lubricant was used.
    - The total non-clinical slippage rate by whether additional lubricant was used.

- The total clinical failure rate (combined breakage and slippage) of PU male test condom (Test condom 2) compared to the NRL male control condom for participants in penis size category 1 (mid shaft lower limit greater than or equal to 128mm).
- Score of each item in EMSEX pleasure scale, the condom pleasure subscale score and the overall scale score in EMSEX pleasure scale from male participants only for each condom type.
- Score of each item and the overall scale score in Quality of Sexual Experience (QSE) Scale from both male and female participant for each condom type.
- The correlation among size, fit and performance of the 2 PU male test condoms and NRL male control condom. Penis size data will be collected by measuring the erectile penile length and girth, condom size and fit data will be collected by answering the participant perceived questionnaire of previous experience and preference of condom and the participant perceived questionnaire of user's perception of comfort and fit of the condoms used in this investigation.

9.5.3.1 Exploratory Endpoint Analyses

For each of the PU male test and NRL male control condoms, the proportion experiencing total clinical failure, clinical breakage, clinical slippage, non-clinical breakage and non-clinical slippage, will be summarised according to whether lubricant was or was not used by descriptive statistics only.

Clinical failure rate for participants in Penis Size Category 1 will be analysed using the same GEE methodology as described for the primary endpoints.

Hence the hypotheses to be tested for this exploratory endpoint are:

H0: PU male test condom 2 total clinical failure rate – NRL male control condom total clinical failure rate ≥ 2.5%

Vs

HA: PU male test condom 2 total clinical failure rate – NRL male control condom total clinical failure rate < 2.5%

From the GEE model, the difference in the proportion of condoms experiencing failure in the test and control condoms will be presented together with an upper one-sided 97.5% confidence limit. If the upper limit is less than 2.5%, this will provide sufficient evidence that the test condom is non-inferior to the NRL control condom with respect to clinical failure in Penis Size Category 1 subgroup.

For each PU male test and NRL male control condom, the score of each item in EMSEX scale (11 items each on a 100-point sliding scale), the condom pleasure subscale score (the mean score of items 9 to 11) and the mean overall scale score in EMSEX pleasure scale (mean score

of all 11 items) collected from male participants only will be summarised using summary statistics.

For each PU male test and NRL male control condom, the score of each item in the quality of sexual experience (QSE) questionnaire (7 items, each on a 7-point scale) and the mean overall scale score of the QSE scale (mean score of all 7 items) will be collected from both male and female participants will be summarised using summary statistics only.

A correlation analysis will be conducted on penis size and condom performance using factors of erect penile size (girth and length), user's previous condom size preference, size of different material condoms used in the investigation, comfort/ fit with condoms against condom performance (total clinical failure, clinical breakage, clinical slippage, non-clinical breakage and non-clinical slippage). A model and figures will be presented demonstrating the correlations.

9.5.4 Descriptive Statistics and Listings

Condom usage will be summarised by treatment group, as the number and percent of couples using 0, 1, 2, 3 condoms etc. This will enable an assessment of whether usage patterns differed for the test and control male condoms.

The event rates for each of the primary and secondary endpoints will be presented descriptively by investigational location.

All data (including number of intercourse episodes for each condom type) will be summarised using descriptive statistics where appropriate, and participant-level data will be provided in data listings.

Further details in relation to secondary and exploratory endpoints will be detailed in the SAP.

9.6 Safety Analysis

9.6.1 Safety Endpoint(s)

Safety endpoints will include incidence of treatment-emergent AEs (TE AEs), ADEs (TE ADEs) and concomitant medications. An AE will be considered treatment emergent if it started since the use of the first condom.

9.6.1.1 Safety Endpoint Analyses

Data listings will be provided for CIP-specified safety data. MedDRA (Version 26.1 or the most recent version if this has changed during the course of the clinical investigation) will be used to code 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) separately for males and females, by treatment group. Treatment-emergent AEs and ADEs will also be summarised by severity and relationship to randomised treatment (condom type) and by relationship to the investigational procedure. Concomitant medication usage will be listed and summarised by coded term separately for males and females, by treatment group.

9.7 Handling of Missing Data and Drop-outs

Any missing data (e.g., due to non-use or data errors) should be ignored in the primary analyses unless patterns are identified which suggest condom type comparisons can be biased. If such patterns are observed, efforts should be made to identify their causes and effects on analyses as per ISO 29943-1:2017 Condoms – Guidance of clinical studies.

There is a potential for data not missing at random (NMAR) due to participants of different condom size preferences testing both the PU male test condoms of different sizes and the NRL male control condom. To assess the amount and patterns of missingness, details for a data review will be documented in the data review plan. A sensitivity analysis will be performed on the data after imputation. Participants missing data for at least one of the three assessment periods will still be included in the mixed model analysis.

10 DATA HANDLING AND RECORD KEEPING

10.1 Case Report Forms

For each enrolled participant an eCRF using fully validated software that conforms to 21 CFR Part 11 requirements, will be maintained. Sites will use an electrotonic data capturing (EDC) system to keep track of study activities and capture data as required in the CIP. Participants will use a web-based platform that is accessible via their phones or tablets at any time, for the questionnaires. Automatic reminders, notifications or e-mails can be customised to increase compliance on participant data entry.

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. eCRFs must be kept current to reflect participant status at each phase during the course of investigation.

The data recorded should be a complete and accurate account of the participant's record collected during the investigation. Participants must not be identified in the eCRF by name or initials. In the eCRF participants will be identified by a participant number in combination with year of birth only, i.e., not by their 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 they will be given access to the eCRF and before the first participant at the site is enrolled. The Investigator must certify that the data entered into the eCRF are complete and correct.

The Investigator agrees to complete the eCRFs in a timely fashion after completion of each participant and make them available to the clinical investigation monitor for full inspection. In addition, any data queries raised should be answered promptly. Following monitoring and data management review of each participant's eCRF, the Investigator or Investigator designee 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.

Upon completion of monitoring and once Data Management has performed all edit checks, the eCRF will be declared clean and all access will be removed.

10.2 Specification of Source Documents

Source data must be available at the site to document the existence of the investigational participants. Source data must include the original documents relating to the investigation, as well as the medical treatment and medical history of the participant.

The Investigator and monitor will identify the data that will be recorded directly on the eCRF (and RedCap for the e-consent) and for this data the eCRF will be considered the source document (i.e., no prior written or electronic record of the data). The clinical investigation monitor will confirm this at the Site Initiation Visit and it will also be documented in the Clinical Monitoring Plan.

Source documents will include, but is not limited to, notes taken at the site, requirements and certification checklists for each visit, data such as demographic data, participation in investigation, eICF, medical history, concomitant medication, SAE, results of examination and medical records contained in the participant records which will be held in the Investigator Site File. The eICF will be saved electronically in pdf form for each participant.

Where source data are in the form of a computer print-out (e.g. laboratory data, results of relevant examinations from an emergency hospital visit) they will be signed and dated by the Investigator or designated person, confirming that the print-out is a true and faithful record of the data for that participant. These print-outs will be filed in the Investigator Site File.

The Investigator agrees to provide direct access to source data for clinical investigation related monitoring, audits, IRB review, and regulatory inspection(s). Direct access to source data requires that the participant 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 with the Sponsor oversight.

All electronic systems will be verified and validated to ensure compliance with Title 21 CFR Part 11 and only authorised personnel will have access to the Electronic Data Capture (EDC) system. 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.

Investigator is responsible for ensuring that accurate data is entered into the EDC system and for reviewing eCRFs, resolving data queries generated, providing missing or corrected data, approving all changes performed on the participant data, and endorsing this data within the EDC 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.

Full details regarding data management including procedures relating to data entry, coding, security, storage and processes to ensure data quality will be described within the Data Management Plan (DMP). The details of data management procedure can be found in DMP.

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 V26.1 (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 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 Clinical Investigation Plan Deviations

Site staff should make the monitor and the Sponsor's Clinical Study Manager aware of any deviations from the Clinical Investigation Plan (CIP) on a timely and consistent basis per the final Protocol Deviation Plan. All identified protocol deviations should be recorded and, following appropriate review, reported to the relevant authority including IRB as required. Waivers for inclusion / exclusion criteria are not allowed.

10.5 Retention of Essential Documentation

The Investigator should retain all essential documents until at least 5 years after the completion of the investigation (defined as last participant 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.

Participant 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 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.

Monitoring includes source data review (SDR) for the eCRF, EDC (including the ePRO), eConsent data. Monitoring may also include 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 participant 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 participant's records for SDR/SDV.

SDR/SDV will include as a minimum verification for all participants, participant identity (year of birth, sex and participant number), record of entry into the clinical investigation and signature of the informed consent. In addition, details of SAEs/SADEs in the participant's AE/SAE forms will be verified. Details included in the participant's forms as a minimum:

- Clinical investigation number, brief description or title of clinical investigation
- Date that the participant gave written consent
- All visit dates
- All SAEs/SADEs
- All concomitant medications

At a visit the eCRFs should be complete and available in order that the accuracy of their completion may be checked. Each completed eCRF for each participant must be signed electronically by the Investigator or Investigator designee, to verify the data and statements submitted. Similarly, all alterations on paper records must be initialled and dated (using the international date format) 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 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 appropriately trained and qualified auditor. Full

consultation with the Investigator will be made prior to and during such audit, which will be conducted according to written procedures.

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

It is the Sponsor's policy to always follow-up on suspected cases of fraud.

12 ETHICAL AND REGULATORY ASPECTS

12.1 Ethics Review and Regulatory Authority Approval

Prior to enrolling participants, the clinical investigation will be reviewed and approved by the central Institutional Review Board (CIRB) in accordance with FDA regulations (21 CFR Part 50, 21 CFR Part 56 and 21 CFR Part 812).

This investigation will only be undertaken when written approval from an independent and appropriately constituted IRB has been obtained. Documented approval must be provided to the Sponsor before any CIP related procedures initiated. The approval letter must contain:

- Name and address of the IRB.
- Date of meeting.
- Sufficient information to identify the version of the CIP and participant information/informed consent.
- Sufficient information to identify the version of other documents reviewed.

This clinical investigation will be submitted to the IRB by the Investigator.

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

Any amendments to the CIP must be submitted to the IRB for approval unless where necessary to eliminate apparent immediate hazards to participants, and any administrative changes must be notified.

The Investigator or designated site staff will notify the IRB within 90 days of the end of the clinical investigation (or within 15 days if the clinical investigation is terminated prematurely).

12.2 Early / Premature Termination of the Investigation

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

- Recall of investigational product(s) when replacements are not available.
- Unacceptable data quality.
- Withdrawal of approval from the Regulatory Authority (RA) (if RA approval is required only) or the IRB.
- Requested by IRB or RA (if required).
- Unresolved non-compliance with applicable regulations, or with the CIP that compromises the participant's rights or safety or the clinical investigation data.

If the decision is made by the Sponsor to terminate the clinical investigation, the involved parties will be notified as per the contractual agreements.

Any decisions to terminate or suspend the study will be notified in writing to the Investigator or designees, the IRB, Regulatory Authority (if required) and the clinicaltrials.gov database.

It is the responsibility of the Investigator to ensure that the reviewing IRB will be informed of the decision to terminate the clinical investigation. The Investigator must comply with the local regulation timeframe for when this notification should be given. An Investigator shall, upon request by a reviewing IRB or RA (if required), provide accurate, complete, and current information about any aspect of the investigation.

If the clinical investigation is terminated early, investigation participants, who have attended screening, will be informed by the Investigator or designee that they are no longer required, that they should discontinue use of the IP (if required) and that if they have any questions, they should consult the site staff. The Investigator or designee will also arrange for appropriate follow-up appointments if required and organise collection of any unused products which have been distributed to the participants. For participants who have completed the investigation they will not be informed that the clinical investigation has been terminated. All data collected up to the point of study termination will be used in an abbreviated Clinical Investigation Report.

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

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

The Sponsor will notify the RA (if required) of the clinical investigation termination.

13 COMPENSATION, INDEMNITY AND INSURANCE

13.1 Clinical Investigation Agreement

Before the investigation commences, a contract between the Sponsor and the CRO, and a contract between the Sponsor and the Site will be signed in which financial aspects of the clinical

investigation (including financial disclosure) as well as responsibilities and obligations are described.

13.2 Insurance

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

13.3 Compensation

The Sponsor, the CRO and Site carry insurance to pay compensation for injury, accident, ill health and death caused by participation in this clinical investigation without regard to proof of negligence.

13.4 Indemnity

The Sponsor will provide appropriate indemnity for the Site and site staff who conduct part or all of this clinical investigation, upon request. The request must be received before the first participant is recruited.

14 REPORTING, PUBLICATION AND PRESENTATION

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

After data collection and analysis are complete, a clinical investigation report will be prepared according to ISO 14155:2020 (Annex D) as part of the Sponsor's commitment to Good Clinical Practice (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

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16 APPENDICES

Appendix 1: Table of Condom Brands and Variants for Selection of Condom Preference Group A and B

Brand Name	Variant/Product Name	Condom Preference Group
Hanx	Hanx Standard	B
	Hanx Large	A
Skyn	Skyn Elite Non Latex Condom	B
	Skyn Elite Large Non Latex Condoms	A
	Skyn Original Latex Free Condoms	B
	Skyn Elite Extra Lube	B
	Skyn Excitation	B
	Skyn Cocktail Club	B
Durex	Durex Condom Performax Intense Natural Latex Condoms, Ultra Fine, ribbed and dotted with delay lubricant	B
	Durex Condom Prolong Natural Latex Condoms - Ultra Fine, ribbed and dotted with delay lubricant	B
	Durex Condom Tropical Natural Latex Condoms, An exciting mix of flavors and colors	B
	Durex Real Feel	B
	Durex ES Regular	B
	DUREX Extra Sensitive - Stimulating Condom	B
	DUREX Extra Sensitive - Smooth Condom	B
	Durex ES - Close	B
	Durex ES - Wide	A
	DUREX Air Original	B
	DUREX Air Wide	A
	DUREX Air Close	B
	Durex Classic	B
	Durex Invisible	B
	DUREX XXL Condoms	A
Trojan	TROJAN™ ENZ™ LUBRICATED CONDOMS	B
	TROJAN™ ENZ™ NON LUBED CONDOMS	B
	TROJAN™ ENZ™ ARMOR	B
	TROJAN™ ULTRA RIBBED	B
	TROJAN™ ULTRA RIBBED ARMOR™	B
	TROJAN™ ULTRA THIN	B
	TROJAN™ ULTRA THIN ARMOR™	B
	TROJAN™ HER PLEASURE™ ARMOR™	B
	TROJAN BARESKIN RAW	B
	TROJAN RAW PURE FEEL	B
	TROJAN™ BARESKIN	B

	TROJAN™ BARESKIN™ SUPRA™ Non-Latex (PU Condom)	B
	TROJAN™ STUDDED BARESKIN™	B
	TROJAN™ ULTRA RIBBED ECSTASY™	B
	TROJAN™ DOUBLE ECSTASY™	B
	TROJAN™ HER PLEASURE™ ECSTASY™	B
	TROJAN™ HER PLEASURE™ Sensition	B
	TROJAN™ PURE ECSTASY™	B
	MAGNUM™ LARGE SIZE CONDOMS	B
	MAGNUM RAW	B
	MAGNUM™ BARESKIN™	B
	MAGNUM™ ECSTASY™	A
	MAGNUM™ THIN	A
	MAGNUM™ RIBBED	B
	MAGNUM™ XL	A
	TROJAN™ ULTRA FIT™ COMFORT FEEL	B
	TROJAN™ ULTRA FIT™ FREEDOM FEEL	B
	TROJAN™ ULTRA FIT™ SENSITIVE TIP FEEL	B
	TROJAN™ ULTRA FIT™ BARE FEEL	B
	TROJAN™ NATURALAMB™	A
	TROJAN™ CHARGED™	B
	TROJAN™ EXTENDED PLEASURE™	B
	TROJAN™ FIRE & ICE™	B
Lifestyles	Ultra Sensitive EO	B
	Ultra Sensitive Platinum SW	B
Lelo Hex	HEX™ 36 Pack	B
Okamoto Wink	Closer	B
	Studded	B
	Slider	B
	Large	B
MyOne	MyOne-Large 57	A
	MyOne-Large 60	A
	MyOne-Large 64	A
	MyOne-Snug 45	B
	MyOne-Snug 47	B
	MyOne-Snug 49	B
	MyOne-Classic 51	B
	MyOne-Classic 53	B
	MyOne-Classic 55	B
ONE	UltraFeel Condoms	B
	Vanish Hyperthin Condoms	B
	Pleasure Plus Condoms	B

	Super Sensitive Condoms	B
	FlavorWaves Condoms	B
	Super Studs Condoms	B
	Legend XL	A
	Tattoo Touch	B
	Glowing Pleasures Condoms	B
Kimono	MicroThin Large	A
	Microthin	B
	Microthin XL	A
Play Boy	Long Play	B
	Ultra Thin Condoms	B
N/A	Do not remember	B
N/A	Do not use condom	B
N/A	Listed other condom (could be any size)	B

Appendix 2: Assignment of Penis Size Category

Penis measurement is recorded from measurements taken by the participant using the penis measuring tool. The girth measurement collected at the mid-shaft point will be used to determine assignment of participants into Penis Size Category 1 (≥128 mm) or Penis Size Category 2 (<128mm). The penis measuring tool considers a colour and letter code for the girth measurements. Each reported measurement falls between an interval of 2mm when converted to a numerical value. The lower limit measurement will be considered to take a conservative approach to calculate the mid-shaft girth size and assignment of participants to a Penis Size category.

To calculate the lower limit of the mid-shaft girth of the penis measurement, the following calculation is required:

59+ 16*(colour code-1) + (2*letter code)-2

Table 16-1 below displays the category assignment.

Table 16-1 Penis Size Categories

Mid-Shaft Girth Size	Penis Size Category
≥128mm	Category 1
<128mm	Category 2

To monitor the enrolment in each penis size category, the penis measurement data will be extracted from the EDC on a regular basis by the data manager and transferred to the Reckitt statistician who will derive the mid-shaft girth size and assign participants to their Penis Size category.