Statistical Analysis Plan

Title: An open label, randomised, 3 - way cross-over, single-centre, clinical investigation to evaluate the effectiveness of benzocaine in two NRL condoms compared with a standard NRL control without benzocaine in prolonging time to ejaculation in healthy adult men who feel they ejaculate too quickly during vaginal sex.

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Confidentiality Statement

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1. Approval Signature Page

With my dated signature, I declare my approval to the procedures described in this document.

[redacted]

Version control of statistical analysis plan after final version.

Version	Date	Reason for change / request / changed by
Final 1	13OCT2023	-
Final 2	24JAN2024	**Amendment No. 1** Specification of the primary target variable. It was defined which IELT values are used in connection with a clinical failure of the condom according to ISO-29943-1 in the context of any analyses and which are consequently classified as not valid and are subsequently excluded. Specification of the primary target variable. It was defined which IELT values are used in connection with a clinical failure of the condom according to ISO-29943-1 in the context of any analyses and which are consequently classified as not valid and are subsequently excluded. The changes concern chapter 11 - paragraph "For primary endpoint" and were made after the first patient in study, but still before collecting any efficacy data. The amendment to the SAP was requested and authorised by the sponsor. [redacted]

Note: After the final version, changes are documented as an amendment to the SAP.

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1 List of abbreviations

Abbreviation	Description
ADE	Adverse Device Effect
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Interval
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRO	Clinical Research Organization
CT	Concomitant Therapy
EMSEX	Event-level Male Sexual
FAS	Full Analysis Set
GLMM	Generalized Linear Mixed Model
ICH	International Council for Harmonisation
IELT	Intravaginal Ejaculation Latency Time
IMSU	Investigational Materials Supplies Unit
IPE	Index of Premature Ejaculation
MedDRA	Medical Dictionary for Regulatory Activities
NRL	Natural Rubber Latex
PGIC	Patient Global Impression of Change
PP	Per Protocol
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Data Verification
SOP	Standard Operating Procedure
SOC	System Organ Class
SPQ	Subject Perceived Questionnaire
STI	Sexually Transmitted Infection
TEADE	Treatment-Emergent Adverse Device Effect
TEAE	Treatment-Emergent Adverse Event
USADE	Unanticipated Serious Adverse Device Effect
WHO	World Health Organization

2 Introduction

The statistical analysis plan (SAP) is a detailed technical extension to the clinical investigation plan (CIP) and follows the principles of the guidelines ICH, E9, E9-R1, ISO 14155:2020 and the relevant standard operating procedure (SOP) DMD_MED_1003_000 "Analysis in Medical Trials" of SGS proderm.

All statistical analyses mentioned in the SAP are performed by SGS proderm.

The SAP is based on the following documents:

- Clinical Investigation Plan (CIP) " An open label, randomised, 3-way cross-over, single-centre, clinical investigation to evaluate the effectiveness of benzocaine in two NRL condoms compared with a standard NRL control without benzocaine in prolonging time to ejaculation in healthy adult men who feel they ejaculate too quickly during vaginal sex.", final version 2.0, dated 08JUN2023.
- Electronic and annotated case report form
    - eCRF final version 1.0 dated 07SEP2023.
    - pCRF final version 2.0 (English version):
        - IELT and EMSEX questionnaire V2.0 dated 18AUG2023
        - IELT Assessment Period Cover Page V2.0 dated 17AUG2023
        - IELT Baseline Cover Page V2.0 dated 13SEP2023
        - IELT Diary V2.0 17AUG2023
        - PGIC V2.0 dated 17AUG2023
        - SPQ V2.0 dated 13SEP2023

3 Investigation design

The investigation design is an open label, randomised, 3-way cross-over, single-centre clinical investigation evaluating the effectiveness of benzocaine in two NRL condoms in prolonging time to ejaculation compared with a standard NRL condom control in healthy male subjects who feel they ejaculate too quickly during vaginal sex.

4 Study objectives

Primary objective

The primary objective of this investigation is to determine the effectiveness of benzocaine, providing ancillary topical action to act as a male genital desensitiser and intended to delay male climax and prolonging the time to ejaculation, of the Test Condom A (5% benzocaine paste condom) compared with the Control NRL Condom (standard NRL condom) at prolonging time to ejaculation.

Secondary objectives

The secondary objectives of this investigation, are as follows:

- To determine the effectiveness of benzocaine, providing ancillary topical action to act as a male genital desensitiser and intended to delay male climax and prolonging the time to ejaculation, of the Test Condom B (3% benzocaine paste condom) compared with the Control NRL Condom at prolonging time to ejaculation.
- To determine the effectiveness of benzocaine, providing ancillary topical action to act as a male genital desensitiser and intended to delay male climax and prolonging the time to ejaculation, of the Test Condom A and Test Condom B compared with the Control NRL Condom at prolonging time to ejaculation for an increase of 2, 3 and 4 minutes.
- To evaluate the sexual pleasure when using Test Condom, A or Test Condom B compared with the Control NRL Condom.
- To evaluate the subject's improvement at "lasting longer" for both the Test Condom A and Test Condom B compared with the Control NRL Condom.
- To evaluate the user acceptability of the Test Condom A, Test Condom B and Control NRL Condom.
- To evaluate the in-use tolerability of the Test Condom A, Test Condom B and Control NRL Condom.
- To evaluate the performance (slippage and breakage) of the Test Condom A, Test Condom B and Control NRL condom when used during vaginal intercourse.
- To assess the safety of the Test Condom A, Test Condom B and Control NRL Condom.

5 Study schedule

Table 5-1 Schedule of Assessments

Visit	Visit 1	Visit 2	Visit 3 & 4	Visit 5
Period	Screening Baseline Period	Assessment Period 1	Assessment Period 2 & 3	Follow-up
Procedure \ Day	Within 28 days prior to Day 1	Day 1	Within 7 days after each condom assessment period	Within 7 days after 3rd condom assessment period
Informed consent	X			
Inclusion / Exclusion[1]	X	X	X	
Demographics	X			
Medical history & prior therapies	X			
Concomitant medication	X	X[9]	X[9]	X[9]
Vital signs	X			X
Physical examination[2]	X	X	X	X
Pregnancy test[3] (subject's female partner)	X	X	X	X
Randomisation		X		
Provide investigation stopwatch	X			
Dispense Investigational Product[4]		X	X	
Collect returned Investigational Product[5]			X	X
Collect returned investigation stopwatch				X
Stopwatch measure and condom use training[6]	X	X	X	
Provide IELT diary, EMSEX pleasure scale, PGIC and SPQ	X[7]	X	X	
Completion of IELT diary	X	X	X	
Completion of EMSEX pleasure scale, PGIC[8] and SPQ[8]		X	X	X

Visit	Visit 1	Visit 2	Visit 3 & 4	Visit 5
Period	Screening Baseline Period	Assessment Period 1	Assessment Period 2 & 3	Follow-up
Procedure / Day	Within 28 days prior to Day 1	Day 1	Within 7 days after each condom assessment period	Within 7 days after 3rd condom assessment period
Review for extent of completion of diary and questionnaires		X[7]	X	X
Adverse Events & Adverse Device Effects and Device Deficiencies	X[9]	X[10]	X[10]	X[10]

1. Eligibility will be confirmed at visit 1 as part of the screening visit. Continued eligibility will be confirmed at each assessment visit (visit 2, 3 and 4).
2. At visit 1, subjects will undergo a penile examination as part of the physical examination. At visit 2, 3, 4 and 5 (assessment period visits and follow-up visit) these will only be performed if necessary in the opinion of the Investigator. The Investigator may conduct physical examination of female partners in any case of AE/ ADE or in the opinion of the Investigator.
3. Subject's female partner of childbearing potential must have a negative pregnancy test at Screening. In cases where subjects have experienced a condom breakage or slippage, their female partner may be subject to a pregnancy test, if deemed necessary by the investigator.
4. Subjects will be provided their allocated condoms (condom type in accordance with the randomisation schedule) at visits 2, 3 and 4. Lubricant will also be supplied, if requested by subjects.
5. Any unused condoms will be returned to the clinical site on visits 3, 4 and 5. All used and unused lubricant will be returned to the clinical site on visit 5.
6. At visit 1, subjects and their female partners will be trained on the stopwatch process and the correct use of the condoms. At visit 2, 3 and 4 (assessment period visits) the training will only be performed if necessary in the opinion of the Investigator.
7. IELT Diary only.
8. PGIC and SPQ can be completed at home or at the next visit.
9. Excludes ADEs and Device Deficiencies.
10. In additional to male subjects' data collection, concomitant medication and AE/ ADE of female partners will be collected through spontaneous reporting or in response to non-leading question to the subject on visit 2, 3, 4 and 5 or observation by the Investigator.

6 Study centres

This is a single centre study performed at SGS proderm GmbH, [redacted]

6.1 Identification-variable in multicentre study

Not applicable.

7 Populations of clinical investigation

A sufficient number of healthy male subjects will be recruited from the clinical site. The expected duration of each subject's participation is a maximum of 19 weeks (from screening to follow-up). There will be 1 clinical site in Germany participating in the clinical investigation. 150 subjects who meet the inclusion/exclusion criteria will be enrolled into the clinical investigation to ensure that a minimum 135 of subjects will be ensured to complete the clinical investigation.

8 Analysis Datasets

The analysis populations will be as follows:

- The safety population will include all randomised subjects who use at least one of the study condoms. The safety population will be used for all baseline summaries and summary of safety data. For the safety population, subjects will be analysed according to treatment received.
- The Full Analysis Set (FAS) will include all randomised subjects who use at least one of the study condoms and who have IELT recorded in at least one of the post-baseline study periods. The FAS will be used for the analysis of all efficacy endpoints. For the FAS, subjects will be analysed according to their randomised treatment.
- The Per Protocol (PP) population will consist of all subjects in the FAS who do not deviate from the protocol in such a way as to impact the evaluation of the primary endpoint. Subjects who do not have an IELT recorded for at least 4 condom uses within a treatment period will be excluded from the PP population for that period. All decisions on exclusions from the PP population will be made prior to database lock. For the PP population, subjects will be analysed according to treatment received.

The final assignment to the FAS and PP population is based on the data review meeting prior to database hardlock. The data review meeting committee is composed of different experts from the sponsor and the CRO.

The disposition of all subjects is shown using a flow chart including all screened subjects.

9 Target variables

The following variables are recorded in the final database and will be presented adequately in the final report.

9.1 Variables evaluated for efficacy

Primary variable

The primary variable is the intravaginal ejaculation latency time (IELT), which is measured in minutes and seconds after the onset of intercourse.

The analysis of the primary endpoint is based on time in minutes and seconds, with time data for all three condom types available from each subject.

The following parameters are collected as part of the primary variable:

Intravaginal ejaculation latency time (IELT) diary - Assessment period 1, 2 and 3

Efficacy variables

- Duration of the intercourse [mm:ss]
- Information of IELT-record [single choice check box]
    - The IELT duration was recorded
    - The IELT duration was not recorded, because the stopwatch did not record.
    - The IELT duration was not recorded, because the intercourse was interrupted.
    - The IELT duration was not recorded, because I did not ejaculate.
    - The IELT duration was not recorded for other reasons, please specify:
        - Specification of "Other" [free text]

Other variables

- Start date and time of intercourse [dd.mm.yyyy – hh:mm] + [single choice check box]
    - Date and time
    - The intercourse did not proceed
        - Specification why not proceed

- Report of condom breakage and condom slippage during the vaginal intercourse or withdrawal from the vagina.[multiple choice check box]
    - Condom broke
    - Condom completely slipped off from the base of the penis during intercourse
    - Condom completely slipped off from the base of the penis during withdrawal from the vagina
        - Hold on to the base of the condom during withdrawal from the vagina [yes/no]
    - No condom breakage or complete condom slippage

- Reaction to condom breakage or complete condom slippage [single choice check box]
    - Removed condom and carried on without a condom
    - Did not proceed further with intercourse.
    - Not applicable since the condom did not break or completely slip

- Usage of lubricant [single choice check box]
    - Yes, the investigation lubricant was used
    - Yes, another type of lubricant was used
        - Specification of other

- No

- Date and time of completing this IELT diary [dd.mm.yyyy – hh:mm]

Secondary variables

The following variables are used to model the secondary endpoints.

IELT diary (translations)

IELT diary - Baseline phase, Assessment period 1,2 and 3 (translations)

- Date and time of the end of intercourse [dd.mm.yyyy – hh:mm]
- If not recorded for other reasons, please specify [free text]
- If yes, provide the name of the condom and its brand [free text]
- If yes, please provide the name of the lubricant and its brand [free text]

EMSEX pleasure scale - Assessment period 1,2 and 3

Efficacy variables

- EMSEX pleasure scale questions measures on a 100mm VAS
  - Q1. The orgasm was outstanding
  - Q2. The timing of my ejaculation (cum) was just right.
  - Q3. The physical sensation on my penis was outstanding.
  - Q4. This sex was very pleasurable.
  - Q5. I was able to maintain my erection throughout the sex act.
  - Q6. The firmness of my erection was ideal during sex.
  - Q7. My penis was comfortable during sex (for example, not pinched).
  - Q8. I was highly physically aroused during sex.
  - Q9. This condom felt like wearing nothing.
  - Q10. This condom helped me enjoy sex.
  - Q11. This condom helped me have better sex.

- Date of completion [dd.mm.yyyy – hh:mm]

Other variables

- The orgasm was outstanding [Number]
- The timing of my ejaculation (cum) was just right [Number]
- The physical sensation on my penis was outstanding [Number]
- This sex was very pleasurable [Number]
- Maintain the erection throughout the sex act [Number]
- The firmness of my erection was ideal during sex [Number]
- Penis was comfortable during sex [Number]
- Highly physically aroused during sex [Number]
- This condom felt like wearing nothing [Number]
- This condom help to enjoy sex [Number]
- This condom help to have a better sex [Number]
- Date and time of completing this IELT Diary and EMSEX Pleasure Scale [dd.mm.yyyy – hh:mm]

Sexual intercourse self-estimation scale

How often do you feel intercourse ended early due to earlier than desired ejaculation?

- Never
- Occasionally (now and then/irregularly)
- Frequently (often/regularly)
- Every time

IELT - EMSEX handout

IELT - EMSEX handout - Return

- Has the subject returned the handout? [yes/no]
- Specify if not returned [free text]

IELT - EMSEX handout - Review

- Has the handout been reviewed? [yes/no]
- Specify if not reviewed [free text]
- Were there at least 4 IELT duration records present? [yes/no]
- Specify if subject did not comply with the minimum diary entries required [free text]

IELT - EMSEX handout - dispense

- Has the subject received the handout and has been instructed how to fill in? [yes/no]
- Specify if not dispensed [free text]

Patient Global Impression of Change (PGIC)

Efficacy variables

PGIC is a scale which assesses the subject's perception of improvement in terms of 'lasting longer' since using the condoms. Thinking about the condoms used and the time before the ejaculated during vaginal sex in the assessment period (up to 4 weeks). The PGIC is a 7-point response scale as follows [single choice check box]:

- Very much better
- Better
- Little better
- No change
- Little worse
- Worse
- Very much worse

Subject perceived questions

Efficacy variables

All efficacy variables are recorded in the following scaling: [Strongly agree/Agree/Neither agree nor disagree/Disagree/Strongly disagree]. Deviating scales are indicated directly after the corresponding questions.

1. The first question is related to the effectiveness of using these condoms [multiple choice check box]:

    - These condoms felt comfortable during use
    - These condoms helped me last longer
    - The fun lasts longer with these condoms
    - These condoms helped me to stay in the moment for longer
    - These condoms helped me to last longer while still enjoying the sensation
    - Using these condoms helped me control my ejaculation/orgasm
    - Using these condoms helped me to enjoy the whole sexual experience
    - Using these condoms made sex more fun
    - I've noticed an improvement in sex since using these condoms
    - I've been able to try out new things and spice things up since using these condoms
    - Using these condoms helped me to be at my sexual best
    - Using these condoms helped me to discover and explore my sexuality
    - Using these condoms helped me to feel more comfortable in my sexuality
    - Using these condoms helped me to have the kind of sex I want
    - Using these condoms helped me to push my boundaries
    - Using these condoms made me feel aroused
    - Using these condoms made me feel excited
    - Using these condoms made me feel energized
    - Using these condoms made me feel desired
    - Using these condoms made me feel sexy
    - Using these condoms made me feel confident
    - Using these condoms helped me feel comfortable in my body
    - Using these condoms helped me feel secure
    - Using these condoms helped me feel accepted
    - Using these condoms helped me feel in control
    - Using these condoms helped reduce my fear and anxiety

2. The second question is related to … [multiple choice check box]:

    - These condoms helped to extend the pleasure for us both
    - Using these condoms made me feel confident in my relationship
    - I feel like using these condoms helped improve the satisfaction of my partner
    - Using this condom helped me to feel prolonged closeness to my partner
    - Using these condoms improved the sexual relationship with my partner

Other variables

3. Did you experience a numbing sensation following application and during use of this condom? [Yes/No]

4. How did you like the numbing effect of the condom? (for completion only if answer yes to the above question 3)

    - Too little for me

- Slightly too little for me
- Just about right
- Slightly too much for me
- Too much for me

5. How fast did you feel the numbing effect of the condom after putting it on? (for completion only if answer yes to the above question 3)

   - Immediately
   - Within seconds
   - After ten seconds to about half a minute
   - After more than a half a minute
   - Not at all

6. On what area(s) on your penis could you feel the numbing effect? See the diagram below for illustration (for completion only if answer yes to question 3)

   - Tip of the penis
   - Shaft of the penis
   - Base of the penis
   - None of these

Global evaluation of effectiveness, tolerance, and usability

All efficacy variables are recorded in the following scale: [very dissatisfied/ somewhat dissatisfied/ neither dissatisfied or satisfied/ somewhat dissatisfied/ very dissatisfied]

- Overall, how satisfied are you with the effectiveness of this condom (how well it works)? [very dissatisfied/somewhat dissatisfied/neither dissatisfied or satisfied/somewhat satisfied/very satisfied]
- Overall, how satisfied are you with the tolerability (gentleness) of this condom on the intimate area? [very dissatisfied/somewhat dissatisfied/neither dissatisfied or satisfied/somewhat satisfied/very satisfied]
- Overall, how satisfied are you with the usability (ease of use) of this condom? [very dissatisfied /somewhat dissatisfied/neither dissatisfied or satisfied/somewhat satisfied/very satisfied]

9.2 Variables evaluated for safety analysis

(Serious) Adverse Events / Adverse Device Effects

(Serious) Adverse events (S)AEs) or Adverse Device Effects (S)ADEs), as reported spontaneously by the subject or observed by the Investigator, recorded in the course of the clinical investigation will be described individually. The following data will be compiled in the (e)CRF:

- Screening number
- AE/ADE number
- Did the subject/partner experience any AEs/ADEs? [yes/no]
- Type of Event [AE/ADE]
- Is this a device deficiency (DD)? [yes/no]
- AE/ADE description [free text]
- Date and time AE/ADE started [dd.mm.yyyy – hh:mm]
- Severity [Mild/Moderate/Severe]

- Any changes in AE/ADE severity? [yes/no]
- Comment the changes if "yes"
- Date of change in severity [dd.mm.yyyy]
- Time of change in severity [hh:mm]
- New severity [mild/moderate/severe]
- Frequency [single episode/intermittant/continuous]
- Action taken (device) [no change/use increased/use reduced/device withdrawn or use stopped/not applicable.
- Action taken (subject) [symptomatic therapy or treatment/subject hospitalised or hospitalisation prolonged/none/other action]
- Specification if "other" was chosen [free text]
- Has the subject been withdrawn from the study due to this AE/ADE? [yes/no]
- Were any concomitant medications taken in association with this AE/ADE? [yes/no]
- Relationship to device (investigator)[causal relationship/probable/possible/not related]
- Is the adverse event/ adverse device effect serious? [yes/no]
- Reasons for being serious [Selection if suitable]
    - Led to death
    - Led to serious deterioration of health that either
        - resulted in a life-threatening illness or injury
        - resulted in a permanent impairment of a body structure or a body function
        - required in-patient hospitalisation or prolongation of existing hospitalization
        - resulted in medical or surgical intervention to prevent life threatening
        - illness or injury or permanent impairment to a body structure or function
    - Led to foetal distress, foetal death or a congenital abnormality or birth defect
    - Device deficiency that may have led to a serious adverse event if
        - Suitable action had not been taken
        - Intervention had not been made
        - If circumstances had been less fortunate
- Is the AE/ ADE ongoing? [yes/no]
- If no, date and time resolved [dd.mm.yyyy – hh:mm]
- Outcome [not recovered / not resolved/recovering or resolving/recovered or resolved/ recovered with sequalae or resolved with sequalae/ fatal/unknown]
- Has the subject ever experienced this AE/ ADE before? [yes/no]
- Age of subject on date of onset of event
- Subject gender
- Current location of device [free text]
- Additional information [free text]
- Date [dd.mm.yyyy]

Note: For AE the MedDRA Coding will be provided. For further details of the listings please see the safety management plan.

Pregnancy test

- Is a pregnancy test deemed necessary by the investigator? [yes/no]
- Results of pregnancy test on partners of childbearing potential [positive/negative/not done]
- Specify the reason if not performed [free text]

Vital Sign

- Were the vital signs measured? [yes/no]
- Specify the reason if no [free text]
- Systolic blood pressure [mmHg]
- Diastolic blood pressure [mmHg]
- Heart rate [b/min]
- Is the body temperature oral or tympanic? [oral/tympanic]
- Body temperature [°C]

Device deficiency details

- Are there any device deficiencies? [yes/no]
- Device deficiency identifier [DD01, DD02, etc.]
- Date/time of device deficiency [dd.mm.yyyy – hh:mm]
- Details for device deficiency [free text]
- For which kit is this device deficiency being reported?
- Could the device deficiency lead to a serious adverse event? [yes/no]

Concomitant Therapies (CT) : subject

Any change of concomitant therapy for subject or partner during the course of the clinical study will be reported individually, the following data will be collected on the (e)CRF:

- Are there any concomitant medications currently being taken by the subject? [yes/no]
- Therapy number (CT01, CT02,…)
- Therapy/Medication (trade name)
- Does the medication belong in one of the groups? [corticosteroids, antibiotics/antihistamines including cough or cold medication/immunosuppressants/anti-inflammatories/anti-hypertensives/cholinesterase inhibitors/others]
- Indication (AE01, AE02,...)
- Is the concomitant treatment a combination drug? [yes/no]
- Details for active ingredient
    - Dose
    - Unit of administration
    - Specification of other
- Details for second active ingredient (Only for combination drugs)
    - Dose
    - Unit of administration
    - Specification of other
- Dose form
- Frequency
- Specification of other 'Frequency' [free text]
- Route
- Specification of other 'Route' [free text]
- Topical therapy in test area(s) [yes/no]
- Start date [dd.mm.yyyy]

- End date [dd.mm.yyyy]
- Ongoing [not applicable/yes]

Note: For prior and concomitant therapies the ATC and WHODrug Coding will be provided. For further details of the listings please see the safety management plan.

Concomitant Therapies (CT): partner

Any change of concomitant therapy for subject or partner during the course of the clinical study will be reported individually, the following data will be collected on the (e)CRF:

- Are there any concomitant medications currently being taken by the partner? [yes/no]
- Therapy number (CT01, CT02,…)
- Therapy/Medication (trade name)
- Does the medication belong in one of the groups? [corticosteroids, antibiotics/antihistamines including cough or cold medication/immunosuppressants/anti-inflammatories/anti-hypertensives/cholinesterase inhibitors/others]
- Indication (AE01, AE02,...)
- Is the concomitant treatment a combination drug? [yes/no]
- Details for active ingredient
    - Dose
    - Unit of administration
    - Specification of other
- Details for second active ingredient (Only for combination drugs)
    - Dose
    - Unit of administration
    - Specification of other
- Dose form
- Frequency
- Specification of other 'Frequency' [free text]
- Route
- Specification of other 'Route' [free text]
- Topical therapy in test area(s) [yes/no]
- Start date [dd.mm.yyyy]
- End date [dd.mm.yyyy]
- Ongoing [not applicable/yes]

Note: For prior and concomitant therapies the ATC and WHODrug Coding will be provided. For further details of the listings please see the safety management plan.

9.3 Other variables

Other relevant variables include the following:

Inclusion and exclusion criteria

- Inclusion criteria met [yes/no/not applicable]
- Exclusion criteria met [yes/no/not applicable]

Demography: subject

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

- Sex
- Age
- Height (X.YY m)
- Weight (X.Y kg)
- Body mass index (BMI) will be calculated as follows: Body weight (kg) / [Height (m)]2 (BMI is > 40 kg/m2, this is an exclusion criterium. Please fill out the termination form.)
- Ethnicity [Caucasian/Asian/Black/Other]
- Specification of other [free text]

Demography: partner

- Sex
- Age
- Is the subject's partner of childbearing potential? [yes/no]

Physical examination: subject and partner

A complete physical examination of the subject will be performed by the investigator or a medically qualified delegate.

- Was the physical examination performed? [yes/no]
- Specify if physical examination assessment not done [free text]
- In the opinion of the investigator, is a physical examination necessary? [yes/no]

The following parameters are measured with the following scale: [normal/ abnormal – not clinically significant/ abnormal - clinically significant/not done]

  - General appearance
  - Skin/subcutaneous tissue
  - Ears/eyes/nose/mouth/throat
  - Head/neck
  - Respiratory/chest
  - Cardiovascular
  - Gastrointestinal
  - Musculoskeletal
  - Neurological
  - Lymph nodes
  - Penile examination (only for subject)

- Specify the reason if any of the assessment where not done [free text]
- Were other body systems examined? [yes/no]
- If yes, which other body system was examined [free text]
- Provide result of examination [normal/ abnormal – not clinically significant/ abnormal - clinically significant]

General questions

- Did the participant observe the 3-day washout period prior to the visit, where no test condom must be used? [yes/no]
- Clarify the reason if no. [free text]
- Did the subject adhere to the rules since last visit? [yes/no]
- Specify the reason if no [free text]
- New adverse event since last visit? [yes/no]

Medical history (for subject and partner)

- Does the subject have any relevant medical or surgical history? [yes/no]
- Medical history: Concomitant diagnosis and therapy

Concomitant Diagnosis

- Diagnosis number (MH01, MH02,…)
- Diagnosis/Surgery
- Start date [dd.mm.yyyy]
- End date [dd.mm.yyyy]
- Ongoing [not applicable/yes]

Risk of STI

- Is the subject at risk for STIs? [yes/no]

Prior therapies

- Was there any therapy / medication prior to study start that needs to be registered? [yes/no]
- Therapy number (PM01, PM02,…)
- Therapy/Medication (trade name)
- Indication (MH01, MH02,...)
- Combination drug? [ticked/not ticked]
- Details for active ingredient
  - Dose
  - Unit of administration
  - Specification of other
- Details for second active ingredient (*Only for combination drugs)*
  - Dose
  - Unit of administration
  - Specification of other
- Dose form
- Frequency
- Specification of other 'frequency' [free text]
- Route
- Specification of other [free text]
- Topical therapy in test area(s) [yes/no]
- Start date [dd.mm.yyyy]
- End date [dd.mm.yyyy]

Note: For the medical history (diagnosis) the MedDRA Coding will be provided. For further details of the listings please see the safety management plan.

Termination

- Date of last contact [dd.mm.yyyy]
- Check one primary reason to indicate end of trial [screen failure/ completed/ drop out]
- Please specify screen failure [did not fulfil inclusion or exclusion criteria/met eligibility criteria but not needed/other]
- Specification of screen failure [free text]
- Please specify drop out [adverse event/serious adverse event/lost to follow-up/ pregnancy/ withdrawal by subject or partner /protocol deviation/other]
- Specification of drop out [free text]
- Who took the decision [Investigator/Subject or partner]
- Date of completion or discontinuation [dd.mm.yyyy]

Visit remarks

- Are there any remarks for the current visit? [yes/no]
- Remark [free text]

Remarks

- Are there any additional non-visit specific remarks?
- Remark [free text]

Product return

- Has the subject returned the investigation stopwatch? [yes/no]
- Specify if not returened [free text]
- Has the subject returned the unused condoms or the empty carton? [yes/no]
- How many unused condoms were returned? [number]
- How many condoms were used? [number]
- Specify if the product was not returned [free text]
- Has the subject returned the used/unused lubricant? [yes/no]
- How many bottles where returned? [number]
- Specify if the product was not returned [free text]

Product training

- Has the subject and their partner received training on how to use the stopwatch? [yes/no]
- Specify if not performed [free text]
- Has the subject and their partner received training on how to use condoms? [yes/no]
- Specify if not performed [free text]
- Was a further stopwatch training necessary? [yes/no]
- If a further stopwatch training was necessary, was it provided? [yes/no]
- Specify if not performed [free text]
- Was a further condom training necessary? [yes/no]
- If a further condom training was necessary, was it provided? [yes/no]

- Specify if not performed [free text]

Product dispense

- Has the subject received the investigation stopwatch? [yes/no]
- Specify if not dispensed [free text]
- Has the subject received the condom carton? [yes/no]
- Specify if not dispensed [free text]
- Was lubricant requested by the subject? [yes/no]
- If, yes. Was lubricant dispensed? [yes/no]
- How many bottles of lubricant were dispensed? [number]
- Specify if not provided [free text]

Product (dispense/return) - Replacement kit

- Did the subject receive a kit replacement? [yes/no]

Product dispense

- Has the subject received the investigation stopwatch?
- Specify if not dispensed [free text]
- Has the subject received the condom carton? [yes/no]
- Specify if not dispensed [free text]

Product return

- Has the subject returned the investigation stopwatch? [yes/no]
- Specify if not returned [free text]
- Has the subject returned the unused condoms? [yes/no]
- How many condoms were returned? [number]
- How many condoms were used? [number]
- Specify if not returned [free text]

10 Data handling

10.1 Transfer of data

After locking the final secuTrial® database, the data management will transfer an export of all data tables to the responsible trial statistician. The trial statistician will get the information that the database is locked by receiving the database hard lock form for signature. Afterwards, the statistician or programmer will generate permanent SAS® master data sets on the server and file the corresponding code.

10.2 Unblinding

Unblinding will take place after locking of the final database. It will be performed in SAS® by combining the imported randomisation list and each SAS® table containing relevant information for the trial. Randomisation numbers are used to match files correctly. The corresponding code will be filed.

Blinded and unblinded data will be listed separately.

10.3 Treatment of baseline values

Within the study, change from baseline in IELT with the 5% Benzocaine condom versus the standard NRL condom, over a 4-week assessment period.

10.4 Categorisations

As part of the analysis, three categorisations of the subjects are carried out.

1. Proportion of subjects who achieve an increase of 2 mins from baseline in IELT in the 5% benzocaine condoms compared to the standard NRL condom are placed in category 1. Those subjects who do not meet this condition are placed in category 0.
2. Proportion of subjects who achieve an increase of 3 mins from baseline in IELT in the 5% benzocaine condoms compared to the standard NRL condom will receive a catagory 1. Those subjects who do not meet this condition are placed in category 0.
3. Proportion of subjects who achieve an increase of 4 mins from baseline in IELT in the 5% benzocaine condoms compared to the standard NRL condom are placed in category 1. Those subjects who do not meet this condition are placed in category 0.
4. Proportion of subjects who achieve an increase of 2 mins from baseline in IELT in the 3% benzocaine condoms compared to the standard NRL condom are placed in category 1. Those subjects who do not meet this condition are placed in category 0.
5. Proportion of subjects who achieve an increase of 3 mins from baseline in IELT in the 3% benzocaine condoms compared to the standard NRL condom will receive a catagory 1. Those subjects who do not meet this condition are placed in category 0.
6. Proportion of subjects who achieve an increase of 4 mins from baseline in IELT in the 3% benzocaine condoms compared to the standard NRL condom are placed in category 1. Those subjects who do not meet this condition are placed in category 0.

10.5 Calculation of derived variables

<u>Difference to baseline</u>

Difference to baseline values will be calculated per subject and assessment time as:

$$Diff\_Variable\_t_{ij} = Variable\_t_{ij} - Variable\_t_{0j}$$

for t_0 = *Baseline*
t_i = *assessment time after application,* $i \in \{1, \ldots, k\}$
j = *subject number* $j = 1,\ldots,n$

Differences from baseline are calculated for the following variables:

- Intravaginal Ejaculation Latency Time (IELT) with Test Condom A, B and Standard NRL condom

Overall proportion of subjects with adverse events / adverse device effects

Proportion of subjects with an (S) AE or S (ADE).

$$Proportion\ \pi = \frac{n_{AE}}{N} \cdot 100$$

for n_{AE} = *number of subjects with at least one (S)AE or (S)AD*
N = *total number of all subjects*

Note: The proportions are given in percent.

Overall proportion of clinical failure event

$$Proportion\ \pi = \frac{n_{CF}}{N} \cdot 100$$

for n_{CF} = *absolute number of clinical breakage or clinical slippage of condom (defined by ISO 29943-1)*
N = *total number condom usage*

Note: The proportions are given in percent.

10.6 Treatment of missing values

In case of the occurrence of missing data, the following rules apply:

IELT

There will be no imputation for missing data. By using a mixed model, subjects who provide data for only one or two of the three assessment periods will be included in the FAS-analysis. For the calculation of mean IELT within an assessment period, only intercourse episodes where IELT is recorded will be included in the analysis.

EMSEX

For the calculation of the mean EMSEX pleasure score (using the 11-items), if more than 5 of the 11 items are missing for a particular coital act, the EMSEX pleasure score will be set to missing for that coital act.

If less equal 5 items are missing, the EMSEX pleasure score is calculated as the mean of the available (answered) item.

No imputation of missing values will be performed.

PGIC

Subjects with a missing PGIC score will be omitted from the respected PGIC analysis.

Subject Perceived Questionnaire

No imputation of missing values will be performed.

Global evaluation of effectiveness, tolerance, and usability

No imputation of missing values will be performed.

10.7 Treatment of outliers

No replacement of outlying data values will be performed.

11 Statistical methods

11.1 Dichotomous and categorical variables

For all dichotomous and categorical variables, absolute and relative frequencies will be calculated if not stated otherwise.

For safety variables – separated by subject and partner:

Two separate counting rules apply for AEs:

- Total number of AEs (possibly counting subjects with several AEs more than once)
- Total and relative number of subjects suffering from at least one AE
- The overall proportion of AE subjects with last safety objective

Frequencies of AEs will be summarized in tables overall, by system organ class (SOC) and preferred term (PT) based on MedDRA Coding (Version 26.1 or higher) including only TE AEs and TE ADEs, which will be summarized (incidence and frequency) separately for males and females, by treatment group.

Two separate counting rules apply for changes in prior and concomitant therapies:

- Total number of changes in concomitant therapies (possibly counting subjects more than once)
- Total and relative number of subjects receiving at least one change in concomitant therapies.

Two separate counting rules apply for concomitant diagnoses:

- Total number of diagnoses/therapies (possibly counting subjects more than once)
- Total and relative number of subjects having at least one diagnosis/therapies. ,

11.2 Continuous and quasi-continuous variables

For all continuous and quasi-continuous variables, the following sample characteristics will be calculated for descriptive presentation:

- count of subjects evaluated (n)
- arithmetic mean (Mean)
- standard deviation (SD)
- median (Median)
- minimum (Min)
- maximum (Max)
- lower confidence interval limit (lower CI limit)
- upper confidence interval limit (upper CI limit).
-

11.3 Graphical presentations

The following plots will be presented:

- Bar charts

11.4 Statistical tests employed

The following methods are employed in this study:

- Generalized mixed model
- Wilcoxon signed rank test

For primary endpoint:

The primary endpoint of the investigation is the change from baseline in IELT with the 5% Benzocaine condom versus the standard NRL condom, over a 4-week assessment period. For each subject, a mean IELT will be calculated across all intercourse episodes within a study period (baseline, assessment period 1, assessment period 2 and assessment period 3) and used for analysis.

For the calculation of the respective mean values, only IELT data points that were generated during a condom-based clinical-failure-free sexual intercourse are taken into account. Ejaculation is to be considered the posterior threshold.

If an IELT value is not considered valid due to the regulation listed in table 19.6 located in the appendix, it is not used in the calculation and is formally considered non-existent in the primary and secondary analyses. This value is also not considered further in any descriptive analysis.

Consequently, the classification of some values as "non-valid" can affect the categorization of the FAS and PP analysis population, as excluded IELT values cannot be evaluated in this consideration either.

The change from baseline in IELT will be analysed using a linear mixed model using data from all three condom groups, with the primary comparison between the 5% benzocaine condom with the standard NRL condom. The model will include fixed effects for treatment and period, a covariate for baseline IELT, and a subject as a random effect. The differences between the 5% benzocaine condom and the standard NRL condom will be presented with a 95% CI and an associated p-value. Statistical significance will be assessed at the two-sided 5% level. No adjustment for multiplicity will be made since there is a single primary comparison (5% benzocaine condom versus standard NRL condom). No assumptions of normality will be checked based on utilizing the Generalized Linear Mixed Model (GLMM) to analyze the primary endpoint. If the model can't handle the violation, a non-parametric model will be used in the worst-case scenario, such as Wilcoxon signed ranks test with Hodges Lehmann estimator for treatment differences.

For secondary endpoints

All secondary endpoints will be evaluated based on comparing the 5% and 3% benzocaine condoms with the standard NRL condom. No adjustment for multiplicity is planned for the secondary endpoints, and so p-values will be interpreted with appropriate consideration of Type I error.

The secondary endpoints of the investigation are:

Change from baseline in IELT with the 3% Benzocaine condom compared to the standard NRL Condom, over a 4-week assessment period.

Proportion of subjects who achieve an increase of 2, 3, 4 mins from baseline in IELT in the 5% and 3% benzocaine condoms compared to the standard NRL Condom.

- The change from baseline IELT with the 3% benzocaine condom compared to the standard NRL condom will be evaluated using the same linear mixed model as for the primary endpoint. The difference in least square means and associated 95% CI will be calculated, with a p-value to assess statistical significance.

- The proportion of subjects who achieve an increase of 2, 3 or 4 mins from baseline in IELT (calculated from the mean across all intercourse episodes within a period) will be calculated

for each condom type. The proportion achieving an increase of 2, 3 or 4 mins will be compared for the 5% and 3% benzocaine condoms versus the standard NRL condom using a GLMM with marginal means under the assumption that the mean of the outcome variable (1=success or 0=failure) follows a binomial distribution. Factors in the model will include fixed effects for treatment and period, and baseline IELT as a covariate. Subject will be included as a random effect. Comparison between the 5% and 3% Benzocaine condoms with the standard NRL condom will be expressed as an odds ratio, with an associated 95% CI and p-value.

A measure of Patient Global Impression of Change (PGIC) at the end of each 4-week assessment period, in subjects using the 5% and 3% benzocaine condoms compared to the standard NRL Condom.

- The PGIC recorded at the end of each condom assessment period will be summarised by condom type, as the number and percentage in each category of the PGIC (Very much better, Better, Little better, No change, Little worse, Worse, Very much worse). A comparison of the PGIC in each of the 5% and 3% Benzocaine condoms versus the standard NRL condom will be performed using a GLMM, assuming a multinomial distribution for the response variable. Factors in the model will include fixed effects for treatment and period. Subject will be included as a random effect. Comparison between the 5% and 3% Benzocaine condoms with the standard NRL condom will be expressed as an odds ratio, with an associated 95% CI and p-value. In the event that some categories of the PGIC have too few subjects for the model to fit, the number of categories in the PGIC responses may be reduced (e.g., better, no change, worse) for purposes of analysis.

A measure of EMSEX pleasure scale at the end of each 4-week assessment period, in subjects using the 5% and 3% benzocaine condoms compared to the standard NRL Condom.

- After each coital act, the mean of the responses on the EMSEX pleasure scale (0 to 100) will be calculated as the sum of responses divided by number of questions answered. For each condom assessment period, a subject-level mean EMSEX pleasure scale will then be derived using data from all coital acts. The EMSEX pleasure scale score will be analysed using a linear mixed model using data from all three condom groups, with comparisons between the 5% and 3% Benzocaine condoms with the standard NRL condom. The model will include fixed effects for treatment and period, and subject as a random effect. The between group differences will be presented with a 95% CI and an associated p-value.

User acceptability, experience and preference of each condom type will be evaluated through subject perceived questions, asked at the end of each 4-week assessment period.

- Responses to SPQs will be summarised for each condom type using descriptive statistics.

The in-use tolerability of each condom type will be evaluated through subject perceived questions, asked at the end of each 4-week assessment period.

A measure of the total clinical failure rate (in percent) of Test Condom A, Test Condom B and Control NRL condom, where as a failure is defined if at least one of the following variables are met (specified according to the high level definition of ISO-29943-1):

1.) Condom breakage or tearing of the condom during intercourse or withdrawal from the vagina
2.) Condom completely slipped off from the base of the penis during intercourse
3.) Condom completely slipped off from the base of the penis during withdrawal from the vagina because user did not hold onto the condom at the base of the penis during withdrawal.

Overall proportion of subjects with Adverse Events/ Adverse Device Effects (AEs/ ADEs), i.e., the occurrence of one or more AEs/ ADEs per subject.

12 Endpoints of clinical investigation

12.1 Generalized linear mixed model

Within the study, the primary endpoint will be analysed using the generalized linear mixed model.

The general form of the model is given by:

$$\dot{y} = \beta_0 + \dot{X}\dot{\beta} + Z\ddot{\gamma}$$

where $\dot{y}$ Model-specific, individually estimated value vector (change from baseline in IELT), $\dot{X}$ is here a matrix of the expression of the corresponding variable for treatment and period, β_0 is a vector containing the fixed intercept and $\dot{\beta}$ is a matrix of fixed effects regression coefficient respectively; $\ddot{\gamma}$ is a matrix of the random effects for each subject. Z is a design matrix that links the respective random effect with the correct indiciduum. The covariance of the random effect will be modelled using a compound symmetry. If this model doesn´t fit, an unstructured covariance can be used instead.
Generalized linear mixed models can be seen as a special cases hierarchical generalized linear model, in which the random effects (subjects) are normally distributed.

12.2 Statistical hypotheses for primary endpoint

The differences between the 5% benzocaine condom with the standard NRL condom will be presented with a 95% CI and an associated p-value. If the GLMM can't handle the violation, then in the worst-case scenario a non-parametric test such as Wilcoxon signed ranks test will be applied.

Therefore, first we consider the null hypothesis under investigation as

H_0: The beta coefficient β_1 of the regression for the group difference from A to Control is equal to 0.

which is tested against the alternative hypothesis.

H_1: The beta coefficient β_1 of the regression for the group difference from A to Control is not equal to 0.

These hypotheses are expressed mathematically by

H_0: $\beta_1 = 0$

H_1 $\beta_1 \neq 0$

where β_1 is the regression coefficient of IELT after 4 weeks.

12.3 Secondary endpoints

In the event of any protocol deviations that warrant exclusion from the FAS, an analysis of the primary endpoint based on the PP population will be performed.

Statistical testing	The change from baseline in IELT will be analysed using a linear mixed model using data from all three condom groups, with the primary comparison between the 5% benzocaine condom with the standard NRL condom. The test is carried out separately for all three condom groups. This analysis is carried out in the FAS population. The analysis is repeated as a sensitivity analysis in the PP population. Analysis of Event-level Male Sexual (EMSEX) pleasure scale is based on a raw data comparison to the baseline of standard NRL condom by GLMM. The test is carried out separately for all three condom groups. Analysis of the proportion values of IELT increasement is based on the proportion of subjects who achieve an increase of 2 minutes on the IELT comparison to the baseline of standard NRL condom by GLMM. Analysis of the proportion values of IELT increasement is based on the proportion of subjects who achieve an increase of 3 minutes on the IELT comparison to the baseline of standard NRL condom by GLMM. Analysis of the proportion values of IELT increasement is based on the proportion of subjects who achieve an increase of 4 minutes on the IELT comparison to the baseline of standard NRL condom by GLMM.

Descriptive analysis	A descriptive analysis is performed for each of the secondary endpoints separately for each condom group. The descriptive analysis of the IELT with the Test Condom B is based on raw data and the differences to baseline for each condom group. The descriptive analysis of measure of Event-level Male Sexual (EMSEX) pleasure scale at the end of a 4-week assessment period and the difference to baseline for Test Condom A. The descriptive analysis of measure of Event-level Male Sexual (EMSEX) pleasure scale at the end of a 4-week assessment period and the difference to baseline for Test Condom B. The descriptive analysis of the proportion values of IELT increasement is based on the proportion of subjects who achieve an increase of 2 minutes on the IELT. The descriptive analysis of the proportion values of IELT increasement is based on the proportion of subjects who achieve an increase of 3 minutes on the IELT. The descriptive analysis of the proportion values of IELT increasement is based on the proportion of subjects who achieve an increase of 4 minutes on the IELT. For all endpoints of 'subject perceived questionnaires' (SPQ) for subject the existing categories are counted for the descriptive analysis. The absolute numbers as well as the percentage distribution are shown. In addition, the upper two categories (strongly agree or agree) are counted together, i.e. the number and percentage of respondents who are in at least one of the two categories. The descriptive analysis of the change in 'patient global impression' is based on each of the PGIC categories at 4 the end of the week. For the endpoint 'User acceptability, experience and preference of each condom' for subject perceived questions at the end of 4 week assessment time iscounted for the descriptive analysis. The descriptive analysis of the in-use tolerability of each condom type will be evaluated for through subject perceived questions at each assessment time based on the safety data. The descriptive analysis of a measure of the total clinical failure rate is based on the raw data for each condom group.

95 % confidence intervals	For the analysis of the IELT with the 5% Benzocaine condom versus the standard NRL condom, 95% confidence intervals and an associated p-value are calculated. The calculation is done for each estimator of each time point separately for each condom group. For the proportion of subjects in the total collective who achieved increase of 2, 3, 4 mins, comparison between the 5% and 3% Benzocaine condoms with the standard NRL condom will be expressed as an odds ratio, with an associated 95% CI. For the analysis of PGIC, the comparison between the 5% and 3% Benzocaine condoms with the standard NRL condom will be expressed as an odds ratio, with an associated 95% CI. For the descriptive analysis of EMSEX pleasure scale the 95%-CI will be displayed. 95%-Hodges-Lehmann-CI in case a GLMM-approach fails.

Sensitivity analysis of selected secondary endpoints	In case of a relevant discrepancy between the sample size of the FAS and the PP population, a sensitivity analysis will be performed on the per protocol (PP) population, which will include data from subjects being compliant with the protocol. The following rule is applied: If the sample sizes of the FAS and PP populations differ by at least 10%, the following endpoints will be analysed on the basis of the PP population. 1) Proportion of subjects who achieve an increase of 2 mins from baseline in IELT in the 3% benzocaine condoms compared to the standard NRL condom. 2) Proportion of subjects who achieve an increase of 3 mins from baseline in IELT in the 3% benzocaine condoms compared to the standard NRL condom. 3) Proportion of subjects who achieve an increase of 4 mins from baseline in IELT in the 3% benzocaine condoms compared to the standard NRL condom. 4) Proportion of subjects who achieve an increase of 2 mins from baseline in IELT in the 5% benzocaine condoms compared to the standard NRL condom. 5) Proportion of subjects who achieve an increase of 3 mins from baseline in IELT in the 5% benzocaine condoms compared to the standard NRL condom. 6) Proportion of subjects who achieve an increase of 4 mins from baseline in IELT in the 5% benzocaine condoms compared to the standard NRL condom. Clinically relevant differences between the results of the FAS and the PP analysis are highlighted and discussed.

12.4 Considerations for non-inferiority and equivalence testing

Not applicable.

12.5 Model Assumptions

No assumptions of normality will be checked based upon the utilization of the Generalized Linear Mixed Model (GLMM) to analyze the primary endpoint. If the model can't handle the violation, then worst case scenario a non-parametric model will be used, such as Wilcoxon signed ranks test with Hodges Lehmann estimator for treatment differences.

12.6 Multiplicity

No adjustment for multiplicity will be made since there is a single primary comparison between the 5% benzocaine condom versus standard NRL condom.

12.7 Sample size and statistical power

In a publication titled "A Multinational Population Survey of Intravaginal Ejaculation Latency Time (Waldinger et al., 2005)", 500 couples were studied in a non-interventional setting over a 4-week period. The mean IELT was 8 minutes (SD = 7.1). Assuming this will be representative of the IELT of men using the standard NRL condom, and that the correlation between repeated measurements within the same subject in the 3 periods of the crossover trial will be 0.5, the table below shows the number of subjects required to detect a clinically meaningful difference of 2 minutes in mean IELT between the Test Condom A (5% Benzocaine paste) and the Control NRL Condom at 90% power, with a significance level of 5% using a two-sided paired t-test.

IELT (mins)		**Number of Subjects**	
Control NRL Condom	Test Condom A (5% Benzocaine paste)	Number to complete	Number randomised (10% drop out)
8	10	135	150

A sample size of 135 subjects will be sufficient to detect a difference of 2 minutes in mean IELT between the Test Condom A and the Control NRL Condom. Allowing for a dropout rate of 10%, 150 subjects will be randomized.

A 2 minute difference in IELT is considered clinically meaningful based on previous studies identified in the published literature. Shabsigh et al (2019) conducted a randomised controlled trial of topical 4% benzocaine wipes for the management of PE defined as self-reported poor control over ejaculation and an IELT of 2 minutes or less. Results showed a statistically significant increase in mean IELT of 164.80 (±11.40 SE) seconds after 1 month of treatment compared to placebo (110.10 s ±9.90 SE). The clinical benefit of a difference in IELT of 1 minute or larger compared to placebo is demonstrated via a patient reported outcome known as the Index of Premature Ejaculation (IPE) whereby the men in the treatment group reported significantly higher sexual satisfaction and greater improvement in distress related to intercourse. For the purposes of relevance to the target population, a larger 2-minute difference in IELT has been selected as the relevant effect for this clinical investigation based on the subjects being healthy adult men as opposed to only men with PE (IELT <2 minutes).

12.8 Randomisation

Randomisation details

Subjects will be allocated to a condom use regime (one of six treatment sequences in a fixed block size of 6 with 34 blocks) according to a computer-generated randomization schedule produced by the CRO. The blocks are each balanced in the ratio 1:1:1.

A randomization schedule will be generated for 204 kits to account for dropouts, overage, replacement and additional randomization codes for IMSU retention samples (which will be retained at Reckitt).

Randomized subjects will be numbered sequentially. The possible range of randomization numbers is accordingly between 1 and 204.

Randomization will be done with SAS software version 9.4-TS-1M7 or higher.

Overview

- Total number of randomization numbers is **204**
- 150 subjects to be randomised + 42 (28% overage) = **192** randomisation numbers with 34 blocks each of size 6
- **12** randomization numbers for IMSU retention (2 complete blocks)
- **192** + **12** = **204**

Information for replacement

Kits will be numbered sequentially. The kit numbers correspond to the subjects' randomisation numbers, as given in the randomization list. Additionally, to this randomisation list, a second list will be generated, which assigns the kit number to the corresponding treatment regimen (n=6 different treatment sequences).

This second list will only contain a treatment regime identifier code (numbers 1 to 6) and will not state the exact sequence of the test products. This list will remain with the Site throughout the study and will be available to the site staff in the case that they need to supply a subject with a replacement kit. This will ensure that same regime is continued by the affected subject, but also does not allow the site staff to draw any conclusions about the exact treatment sequence as they only have access to the treatment regime identifier.

In the case that a kit or single carton is damaged, the site staff will replace the whole kit or carton, respectively. If a single condom packaging is damaged the whole carton is replaced. The replacement will be recorded in the eCRF via a remark. The damaged kit/carton is photographed and stored at the site until shipment to the sponsor together with the unused investigational products (see CIP section 5.9).

A replaced kit cannot be used for another subject.

12.9 Interim analyses

No interim analysis is planned.

12.10 Subgroup analyses

Not applicable.

12.11 Adjustment for covariates

Not applicable.

12.12 Confidence intervals

Confidence intervals (CI) for means are given where suitable. They are computed two-sided based on asymptotic normality at a confidence level of 95 % =100· (1- α) %, if not stated otherwise:

$$CI = \mu \pm c \cdot \frac{\sigma}{\sqrt{n}}$$

for *μ = Sample mean for the respective variable*
$c = t_{1-\frac{\alpha}{2};n-1}$ *Percentile of the t distribution*
□ = Sample standard deviation for the respective variable
n = Sample size

Confidence intervals (CI) for odds ratio are given where suitable. They are computed two-sided based on asymptotic normality at a confidence level of 95 % =100· (1- α) %:

This calculator uses the following formulae to calculate the odds ratio (or) and its confidence interval.
or = a·d / b·c, where:

- a is the number of times both A and B are present,
- b is the number of times A is present, but B is absent,
- c is the number of times A is absent, but B is present,
- d is the number of times both A and B are negative.

Contingency table	A	1	0	Marginal sum
B				
1		a	b	a+b
0		c	d	c+d
Marginal sum		a+c	b+d	a+b+c+d

To calculate the confidence interval, we use the log odds ratio

$$log(or) = log(a \cdot d / b \cdot c)$$

with its standard error

$$SE(log(or)) = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

The confidence interval is calculated as:

$$CI = \exp(\log(or) \pm Z_{\alpha}/2 \cdot \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

where $Z_{\alpha}/2$ is the critical value of the normal distribution at $\alpha/2$ (e.g., for a confidence level of 95%, the type I error is, $\alpha = 0.05$ and its critical z-value is $Z = 1.96$).

Note: The logarithms included in the formulae above are natural logarithms, i.e., log base e, sometimes denoted as $ln(\,)$.

Confidence Intervals for Wilcoxon signed rank test are calculated according to Hodges-Lehmann. This is done according to the following method:

Let $[\lambda_{*}, \lambda^{*}]$ be the exact $100 \cdot (1-\alpha)\%$ confidence interval for the median difference. Let $M = \frac{N(N+1)}{2}$ and let $A_{[1]} \leq A_{[2]} \leq A_{[\ldots]} \leq A_{[M]}$ be the M averages, $\frac{(d_i+d_j)}{2}$ for all $i \leq j$, sorted in ascending order.

The lower confidence interval is formed by setting $\lambda_{*} = A_{[i]}$ where $[i] = 1 + t_{*}$ where t_{*} rounds down t_{*} to the nearest integer.

The upper confidence interval is formed by setting $\lambda^{*} = A_{[i]}$ where $[i] = t^{***}$ where t^{***} rounds up t^{*} to the nearest integer.

t_{*} is determined by finding a value for t_{*} so that the formula satisfies the following condition:

$$\Phi\left(\frac{t_{*} - \frac{N \cdot (N+1)}{4}}{\sqrt{\frac{N \cdot (N+1) \cdot (2N+1)}{24}}}\right) = \frac{\alpha}{2}$$

t^{*} is determined by finding a value for t^{*} so that the formula satisfies the following condition:

$$1 - \Phi\left(\frac{t^{*} - \frac{N \cdot (N+1)}{4}}{\sqrt{\frac{N \cdot (N+1) \cdot (2N+1)}{24}}}\right) = \frac{}{2}$$

The confidence intervals for the proportion values are calculated according to the Wilson Score method. The following calculation method is used for this purpose:

$$CI = \frac{1}{1 + \frac{c^2}{n}} \cdot (\hat{p} + \frac{c^2}{2n} \pm c \cdot \sqrt{\frac{\hat{p} \cdot (1-\hat{p})}{n} + \frac{c^2}{4n}}).$$

For $c = \phi^{-1} \cdot (1 - \frac{\alpha}{2})$ where $\frac{\alpha}{2}$ is the two sided error level and ϕ^{-1} denotes the quantile function of the standard normal distribution, i.e. the inverse function of its distribution function Φ.

$\hat{p}$ denotes the estimated proportion value.

12.13 Conventions

The number of decimal places for raw data and calculated values are determined by an internal guideline. The presentation of target variables follows the SGS proderm style guide.

For frequency tables, only those categories for which there is at least one subject represented will be included in the tables, except the intention is the direct visual comparison between categories.

13 Preparation and control of program code

All SAS® Code used for statistical analysis is the responsibility of the trial statistician but may be delegated to a programmer. The statistical output programmed in SAS® version 9.4 is based on this SAP. All statistical analysis programs are subjected to a version control system so that changes in the program can be tracked. The output log files of SAS® are searched automatically for errors and these are written, if available, automatically into an additional file. The log and error file of the final analysis is saved.

Controlling of program codes and statistical outputs is done by a person responsible for quality control e.g., a 2nd statistician according to SOPs DMD_MED_1003_000 "Analysis in medical trials" and 12STA006.

The control follows a standardized scheme, which can be extended if necessary. The results of the control are saved in a separate Excel document signed.

The primary statistician implements the control's observations, documenting all actions taken.

All program codes and statistical outputs will be controlled based on a risk assessment. The recommended quality control strategy will be examined, and its appropriateness verified until release.

14 Formats

Statistical outputs will be presented in British English. Fonts point sizes of at least 8 will be used.

Data presented in listings and tables will be formatted as follows:

- alphanumeric data will be middle justified
- numeric values and date values will be middle justified
- column heading will be aligned centre for alphanumeric data, for numeric values and date values
  - If local conditions make it necessary, the alignment of the headings and data may differ.

Units will be given in the column heading for numeric values where appropriate.

Any abbreviations in tables and figures will be explained in footnotes unless they are already specified in the abbreviation list of the report.

Values in the data listing will be presented as recorded in the (e)CRF, except technical variables. Technical variables are labelled with "tc_" in the variable name in the (e)CRF and may not be shown in the data listing.

Estimated means and standard deviations for continuous or quasi-continuous variables will be printed to one more decimal place than the individual value of measurement. Percentage values will be printed with one decimal place.

All p-values will be given with four digits to the right of the decimal point. In case a rounded value of p=0.0000 is computed by SAS®, 'p<0.0001' will be printed.

15 Changes from clinical investigational plan

No changes from Clinical Investigation Plan to SAP occurred.

16 Software utilized

Task	Software	Version
Sample Size Estimation	SAS® for Windows nQuery Advisor 5.0 or other	9.4 or higher
Statistical Analysis	SAS® for Windows	9.4 or higher
Clinical database	secuTrial®	6.5.0.6 or higher

17 Topline results

The topline results include:

- Allocation of subjects in the respective study populations (SP, FAS, PP)
- Statistical analysis of the primary endpoint (FAS and PP)
- Selection of secondary efficacy endpoint(s) to support the primary endpoint (FAS and PP*)
    - Change from baseline in IELT with the 3% Benzocaine condom compared to the standard NRL Condom
    - Proportion of subjects who achieve an increase of 2 mins from baseline in IELT in the 3% benzocaine condoms compared to the standard NRL condom.
    - Proportion of subjects who achieve an increase of 3 mins from baseline in IELT in the 3% benzocaine condoms compared to the standard NRL condom.
    - Proportion of subjects who achieve an increase of 4 mins from baseline in IELT in the 3% benzocaine condoms compared to the standard NRL condom.
    - Proportion of subjects who achieve an increase of 2 mins from baseline in IELT in the 5% benzocaine condoms compared to the standard NRL condom.
    - Proportion of subjects who achieve an increase of 3 mins from baseline in IELT in the 5% benzocaine condoms compared to the standard NRL condom.
    - Proportion of subjects who achieved an increase of 4 mins from baseline in IELT in the 5% benzocaine condoms compared to the standard NRL condom.

- Counts and percentages of (S)AEs (SP)
- Description of events in conjunction with causality to the study, pattern, intensity and outcome of (S)AEs (SP)

* Provided that the rule for sensitivity analysis from chapter 12.2 applies.

18 References

ICH-Guideline Structure and Content of Clinical Study Reports (ICH E3, final signed off, 30 November 1995)

ICH-Guideline Guideline for Good Clinical Practice (ICH E6 (R2), final signed off, 14 Jun 2017)

ICH-Guideline Statistical Principles for Clinical Trials (ICH E9, final signed off, 5 February 1998)

ICH E9 (R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (ICH E9 (R1), Date for coming into effect, 30 July 2020)

ISO 14155:2020: Clinical investigation of medical devices for human subjects — Good clinical practice (Third Edition; July 2020)

Shabsigh et al., Randomized, place-controlled study to evaluate the efficacy, safety, and tolerability of benzocaine wipes in subjects with premature ejaculation, Journal of Men's Health, 2019, Vol 15(3): e80-e88.

Waldinger MD, Quinn P, Dilleen M, Mundayat R, Schweitzer DH, Boolell M. A Multinational Population Survey of Intravaginal Ejaculation Latency Time. J Sex Med 2005; 2: 492-497

Overview

The summary of the statistical analysis scheme is presented in the following table:

Target variables	Population	Graphs	Statistical methods
Disposition of subjects	SP	Flowchart	
Disposition of investigational products	SP	Flowchart	
Baseline characteristics	SP		
childbearing potential, ethnicity, physical examination	SP	--	Counts and percentages
Age, height, weight, BMI	SP	--	Descriptive statistics
Medical history	SP	--	Counts and percentages
Primary variable* IELT with the 5% Benzocaine condom A	FAS*, PP**	Bar chart	Descriptive statistics 95 % Confidence Intervals GLMM or Wilcoxon signed ranks test
Secondary variable(s)	FAS		
IELT with the 3% Benzocaine condom B	FAS**, PP**	Bar chart	Descriptive statistics 95 % Confidence Intervals GLMM or Wilcoxon signed ranks test
EMSEX Pleasure Scale for Test Condom A OR B against standard NRL condom	FAS**	--	Descriptive statistics 95 % Confidence Intervals GLMM or Wilcoxon signed ranks test
Patient Global Impression of Change (PGIC)	FAS**	--	Counts and percentages GLMM or Wilcoxon signed ranks test 95 % Confidence Intervals
Subject perceived questions	FAS**		Counts and percentages

Target variables	Population	Graphs	Statistical methods
Proportion of subjects who achieve an increase of 2 mins from baseline in IELT	FAS**, PP***	--	Descriptive statistics Counts and percentages GLMM or Wilcoxon signed ranks test 95 % Confidence Intervals
Proportion of subjects who achieve an increase of 3 mins from baseline in IELT	FAS**, PP***	--	
Proportion of subjects who achieve an increase of 4 mins from baseline in IELT	FAS**, PP***	--	
Total clinical failure rate	FAS**	--	Descriptive statistics Counts and percentages

*: Confirmatory hypothesis testing
**: No confirmatory hypothesis testing, part of secondary analysis
***: Provided that the rule for sensitivity analysis from chapter 12.2 applies.

Additional tables and figures are acceptable for illustrative purposes. Additional statistical tests can be performed, if reasons are given in the final report. The corresponding p-values have to be interpreted purely descriptive in the context of an explorative data analysis.

Examples of crucial tables, listings and figures can be seen in Chapter 19.

19 Appendices

19.1 Mock listing

A complete listing of subjects raw data will be integrated in the final report. The layout will be according to the following mock listings:

Listing general data

Random/Subject No.	[Variable 1 NUMERIC]	[Variable 2 DATE]	[Variable …]	[Variable N ALPHANUMERIC]
1	[VALUE]	[VALUE]		[VALUE]
2	[VALUE]	[VALUE]		[VALUE]
...	...	...		...
n-1	[VALUE]	[VALUE]		[VALUE]
n	[VALUE]	[VALUE]		[VALUE]

Listing demographic data

Random/Subject No.	Subject ID	Screening Date	Age [years]	Height [cm]	Weight [kg]
1	X	DDMMMYYYY	X	X	X
2	X	DDMMMYYYY	X	X	X
...	...	...	...	...	...
n-1	X	DDMMMYYYY	X	X	X
n	X	DDMMMYYYY	X	X	X

Listing efficacy data (derandomized)

Random/ Subject No.	Time	Product	Variable 1 [<unit>]	Variable 2 [<unit>]	Variable 3 [<unit>]	Variable 4 [<unit>]
1	[TIME 1]	[PRODUCT 1]	X	X	X	X
	[TIME…]	[PRODUCT 1]	X	X	X	X
	[TIME N]	[PRODUCT 1]	X	X	X	X
2	[TIME 1]	[PRODUCT N]	X	X	X	X
	[TIME…]	[PRODUCT N]	X	X	X	X
	[TIME N]	[PRODUCT N]	X	X	X	X

19.2 Mock tables

Tables of the following kind will be presented to illustrate the efficacy analysis in the final report of the study:

Mock table for descriptive statistics of (quasi) continuous variables - baseline characteristics

	Descriptive Statistics						95% CI	
	n	Mean	Standard Deviation	Minimum	Median	Maximum	Lower limit	Upper limit

	Descriptive Statistics						95% CI	
	n	Mean	Standard Deviation	Minimum	Median	Maximum	Lower limit	Upper limit
<Variable [<unit>]>								
SP	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
FAS	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
PP	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX

Mock table for descriptive statistics of (quasi) continuous variables – baseline characteristics

	Descriptive Statistics						95% CI	
Visit	n	Mean	Standard Deviation	Minimum	Median	Maximum	Lower limit	Upper limit
<Variable [<unit>]> [[FAS/PP] (N = n)]								
IP 1	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
IP 2	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
<Variable [<unit>]> [[FAS/PP] (N = n)]								
IP 1	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
IP 2	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
<Variable [<unit>]> [[FAS/PP] (N = n)]								
IP 1	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
IP 2	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX

Mock table of counts and percentages of categorical variables – baseline characteristics

	[Category 1]		[Category …]		[Category N]		Total	
Visit	n	(%)	n	(%)	n	(%)	n	(%)
<Variable [<unit>]> [[FAS/PP] (N = n)]								
SP	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
FAS	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
PP	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
<Variable [<unit>]> [[FAS/PP] (N = n)]								
SP	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
FAS	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
PP	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
<Variable [<unit>]> [[FAS/PP] (N = n)]								
SP	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
FAS	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
PP	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)

Mock table of counts and percentages of categorical variables – baseline characteristics

	[Category 1]		[Category …]		[Category N]		Total	
Visit	n	(%)	n	(%)	n	(%)	n	(%)
<Variable [<unit>]> [[FAS/PP] (N = n)]								
IP 1	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
IP 2	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
<Variable [<unit>]> [[FAS/PP] (N = n)]								
IP 1	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
IP 2	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
<Variable [<unit>]> [[FAS/PP] (N = n)]								
IP 1	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
IP 2	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)

Mock table for descriptive statistics of (quasi) continuous variables – efficacy variables

Visit	Descriptive Statistics						[95;99]% CI	
	n	Mean	Standard Deviation	Minimum	Median	Maximum	Lower limit	Upper limit
<Variable [<unit>]> [[FAS/PP] (N = n)] – IP 1								
Time 1	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
Time …	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
Time N	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
<Variable [<unit>]> [[FAS/PP] (N = n)] – IP 2								
Time 1	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
Time …	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
Time N	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX

Mock table for descriptive statistics of (quasi) continuous variables – difference to baseline

Visit	Descriptive Statistics						[95;99]% CI	
	n	Mean	Standard Deviation	Minimum	Median	Maximum	Lower limit	Upper limit
<Variable [<unit>]> [[FAS/PP] (N = n)] – IP 1								
Time 1	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
Time …	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
Time N	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
<Variable [<unit>]> [[FAS/PP] (N = n)] – IP 2								
Time 1	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
Time …	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
Time N	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX

Mock table of counts and percentages of scores for dichotomous and categorical variables

Visit	[Score 1]		[Score …]		[Score N]		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
<Variable [<unit>]> [[FAS/PP] (N = n)] – IP 1								
Time 1	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
Time …	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
Time N	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
<Variable [<unit>]> [[FAS/PP] (N = n)] – IP 2								
Time 1	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
Time …	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
Time N	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
<Variable [<unit>]> [[FAS/PP] (N = n)] – IP N								
Time 1	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
Time …	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
Time N	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)

Mock table of counts and percentages of adverse events: preferred term, intensity.

		Mild				Moderate				Severe				Total				Total
Population	PT	R0	R1	R2	R3	R0	R1	R2	R3	R0	R1	R2	R3	R0	R1	R2	R3	R0+R1+R2+R3
	PT 1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	PT 2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

R0=none, R1=possible, R2=probable, R3=definitive

Mock table for results of Wilcoxon signed rank test for assessment time comparisons

		Results of Wilcoxon signed rank test for comparisons of assessment times on <Variable Name> [<unit>]						
Population	**Time**	**Comparison**	**n (Pairs)**	**n with < Product /TIME 1>- < Product/TIME 2> < 0**	**n with < PRODUCT/TIME 1>- < PRODUCT/TIME 2> > 0**	**Mean Difference**	**Median Difference**	**p-Value**
FAS (N = n)	<TIME X>	<TIME X> vs. <TIME Y>	X	X	X	XX.XX	XX.XX	X.XXXX
PP (N = n)	<TIME X>	< TIME X> vs. < TIME Y>	X	X	X	XX.XX	XX.XX	X.XXXX
Note on the result: **bold p-Value: significant (p ≤ 0.05)**								

Mock table for results of GLMM for product comparisons

Results of generalised linear mixed modell for product comparison (FAS or PP)						
Parameter	**Level of categorial parameter**	**Regression coefficient**	**SE**	**DF**	**t-value**	**p-value**
Intercept		XX.X	XX.XX	XX	XX.X	**X.XXXX**
Parameter 1		XX.X	XX.XX	XX	XX.X	X.XXXX
Parameter 2	Parameter 2 - Level 1	XX.X	XX.XX	XX	XX.X	**X.XXXX**
Parameter 2	Parameter 2 - Level 2	XX.X	XX.XX	XX	XX.X	X.XXXX
Parameter 2	Parameter 2 - Level 3	0 (Reference)				
Parameter 3		XX.X	XX.XX	XX	XX.X	**X.XXXX**
Note on the result: **bold p-Value: significant (p ≤ 0.05)**						

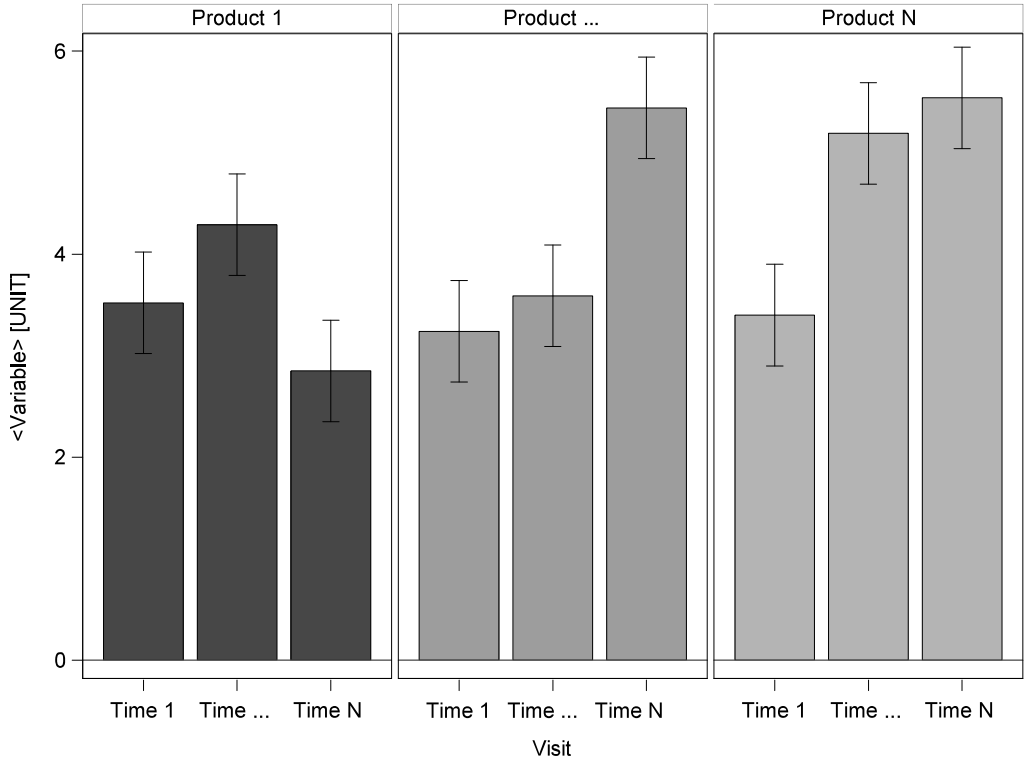
Mock table for odds ratio for product comparisons

Results of odds ratio for product comparison (FAS or PP)				
Effect	**Unit**	**Odds ratio estimator**	**95% Confidence limits**	
			Lower limit	**Upper Limit**
Treatment A vs C	1.0	XX.X	XX.XX	XX.XX
Treatment B vs P	1.0	XX.X	XX.XX	XX.XX
Note on the result: **bold p-Value: significant (p ≤ 0.05)**				

19.3 Mock graphs

Graphs of the following kind will be presented to illustrate the efficacy analysis in the final report of the study:

Mock graph for bar charts with error bars on <variable name> [<unit>] by product



19.4 Tables planned

The following tables with the respective descriptive statistics to deliver the data basis for the results part of the report (Chapter 11 and 14) are planned:

14.1. Demographic, baseline *and compliance data for subject and partner (if available) (SP)*

Table 14.1.1	Counts and percentages of subjects per analysis set
Table 14.1.2	Counts and percentages of protocol deviations
Table 14.1.3	Counts and percentages of eligible subjects
Table 14.1.4	Counts and percentages of premature terminations
Table 14.1.5	Descriptive statistics for demographics [age, body height, weight and BMI at screening]
Table 14.1.6	Counts and percentages of ethnicity at screening
Table 14.1.7	Counts and percentages of childbearing potential at screening
Table 14.1.8	Counts and percentages of result of pregnancy test at screening and termination
Table 14.1.9	Counts and percentages of physical examination
Table 14.1.10	Descriptive statistics of vital signs at screening and termination
Table 14.1.11	Descriptive statistics for sexual intercourse self-estimation scale at screening

Table 14.1.12 Counts and percentages of concomitant diagnoses and subjects with concomitant diagnoses at screening

Table 14.1.13 Counts and percentages of concomitant therapies and of subjects with concomitant therapies at screening

Table 14.1.14 Descriptive statistics of investigational product information

14.2. Efficacy *Data*

14.2.1. Primary Variable

Table 14.2.1.1 Descriptive statistics for IELT for the 5% Benzocaine condom compared to the standard NRL condom (FAS/PP)

Table 14.2.1.2 Descriptive statistics for difference to baseline for IELT of 5% Benzocaine condom compared to the standard NRL condom (FAS/PP)

Table 14.2.1.3 Results of GLMM for comparisons of difference to baseline for IELT of 5% Benzocaine condom against the standard NRL condom (FAS/PP*)

Figure 14.2.1.1 Bar chart of IELT with the 5% Benzocaine condom and standard NRL condom for primary hypothesis (FAS/PP)

Figure 14.2.1.2 Bar chart of difference to baseline for IELT with the 5% Benzocaine condom and standard NRL condom for primary hypothesis (FAS/PP)

*: No confirmatory hypothesis testing

14.2.2 Secondary Variables for subject and partner (if available) (FAS)

Table 14.2.2.1 Descriptive statistics for IELT for the 3% Benzocaine condom compared to the standard NRL condom (FAS/PP)

Table 14.2.2.2 Descriptive statistics for difference to baseline for IELT of 3% Benzocaine condom compared to the standard NRL condom (FAS/PP)

Table 14.2.2.3 Results of GLMM for comparisons of difference to baseline for IELT of 3% Benzocaine condom against the standard NRL condom (FAS*/PP*)

Table 14.2.2.4 Descriptive statistics for proportion of subjects who receive an decrease of 2 minutes in IELT in difference to baseline with the 3% Benzocaine condom compared to the standard NRL condom (FAS/PP**)

Table 14.2.2.5 Results of GLMM for comparisons of proportion of subjects who receive an decrease of 2 minutes in IELT in difference to baseline with the 3% Benzocaine condom against the standard NRL condom (FAS/PP**)

Table 14.2.2.6 Descriptive statistics and odds ratio for proportion of subjects who receive an decrease of 2 minutes in IELT in difference to baseline with the 5% Benzocaine condom compared to the standard NRL condom (FAS/PP**)

Table 14.2.2.7 Results of GLMM for comparisons of proportion of subjects who receive an decrease of 2 minutes in IELT in difference to baseline with the 5% Benzocaine condom against the standard NRL condom (FAS/PP**)

Table 14.2.2.8 Descriptive statistics and odds ratio for proportion of subjects who receive an decrease of 3 minutes in IELT in difference to baseline with the 3% Benzocaine condom compared to the standard NRL condom (FAS/PP**)

Table 14.2.2.9 Results of GLMM for comparisons of proportion of subjects who receive an decrease of 3 minutes in IELT in difference to baseline with the 3% Benzocaine condom against the standard NRL condom (FAS/PP**)

Table 14.2.2.10 Descriptive statistics and odds ratio for proportion of subjects who receive an

*: No confirmatory hypothesis testing

**: Provided that the rule for sensitivity analysis from chapter 12.2 applies.

14.3. Safety Data (SP)

14.3.1. Display of adverse events of subject and partner

Table 14.3.1.1	Counts and percentages of TE-AEs/ADEs and subjects with TE-AEs/ADEs
Table 14.3.1.2	Counts and percentages of AEs/ADEs and subjects with TE-AEs/ADEs by SOC and PT
Table 14.3.1.3	Counts and percentages of TE-AEs/ADEs: relationship to IP
Table 14.3.1.4	Counts and percentages of TE-AEs/ADEs: severity
Table 14.3.1.5	Counts and percentages of TE- AEs/ADEs: action taken (subject)
Table 14.3.1.6	Counts and percentages of TE-AEs/ADEs: outcome
Table 14.3.1.7	Counts and percentages of subject withdrawn due to TE-AE/ADE
Table 14.3.1.8	Counts and percentages of TE-AEs/ADEs: serious adverse event

14.3.2. Display of deaths, other serious and significant adverse events (if applicable)

14.3.3. Narratives of deaths, other serious and certain other significant adverse events (if applicable)

14.3.4. Display of device deficiency *(if applicable)*

Table 14.3.4.1	Counts and percentages of DDs and subjects with DDs
Table 14.3.4.2	Counts and percentages of DDs which might have led to a serious adverse event

14.3.5. Abnormal Laboratory Value Listing

Not applicable

19.5 Listings planned

All data collected within the scope of the clinical investigation are mapped within the listings. This includes collected raw data as well as derived data.

Technical variables (indicated by "tc_" in the variable name) are an exception here, as they only contain redundant information and can therefore be omitted without any loss of information.

19.6 Additional tables

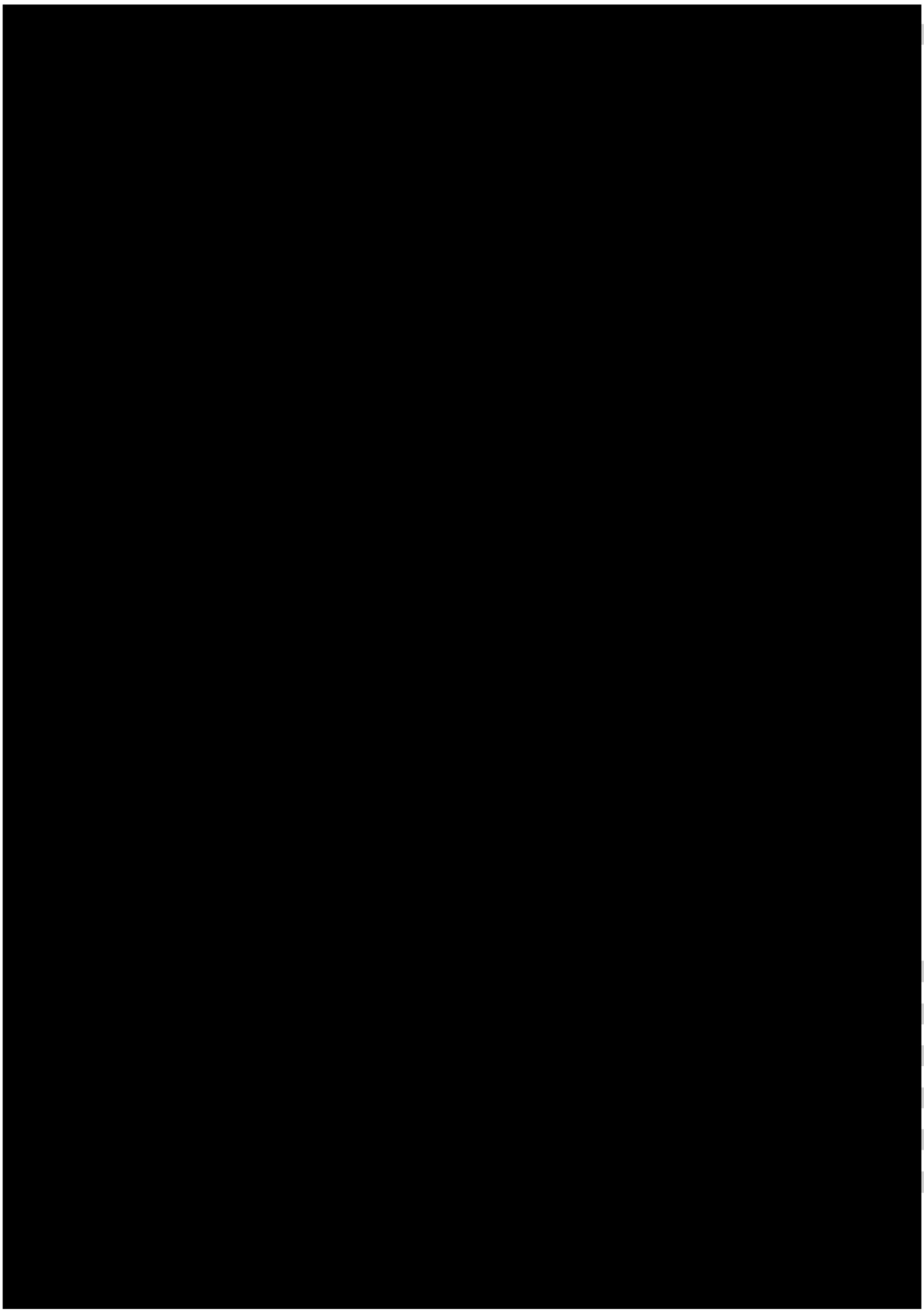
Based on the possible scenarios, the following rules apply to the use of the corresponding IELT values:

IELT duration recorded	Clinical Breakage[1]	Clinical Slippage[2]	Clinical Slippage[3]	Non-Clinical Slippage[4]	No condom breakage or complete condom slippage	Clinical Failure	IELT duration used for analysis
Breakage Scenarios:							
Yes	Yes	Yes	Yes	Yes	Ticked[5] or Not ticked	Yes	No
Yes	Yes	Yes	Yes	No	Ticked[5] or Not ticked	Yes	No
Yes	Yes	Yes	No	Yes	Ticked[5] or Not ticked	Yes	No
Yes	Yes	Yes	No	No	Ticked[5] or Not ticked	Yes	No
Yes	Yes	No	Yes	Yes	Ticked[5] or Not ticked	Yes	No
Yes	Yes	No	Yes	No	Ticked[5] or Not ticked	Yes	No
Yes	Yes	No	No	Yes	Ticked[5] or Not ticked	Yes	No
Yes	Yes	No	No	No	Ticked[5] or Not ticked	Yes	No
Non-Breakage Scenarios:							
Yes	No	Yes	Yes	Yes	Ticked[5] or Not ticked	Yes	No
Yes	No	Yes	Yes	No	Ticked[5] or Not ticked	Yes	No
Yes	No	Yes	No	Yes	Ticked[5] or Not ticked	Yes	No
Yes	No	Yes	No	No	Ticked[5] or Not ticked	Yes	No
Yes	No	No	Yes	Yes	Ticked[5] or Not ticked	Yes	Yes[7]
Yes	No	No	Yes	No	Ticked[5] or Not ticked	Yes	Yes[7]
Yes	No	No	No	Yes	Ticked[5] or Not ticked	No	Yes[7]
Non-Breakage and Non-Slippage Scenarios:							
Yes	No	No	No	No	Ticked	No	Yes
Yes	No	No	No	No	Not ticked[6]	No	Yes

Notes from table:

1. Condom broke during the vaginal intercourse or withdrawal from the vagina.
2. Condom completely slipped off from the base of the penis during intercourse.
3. Condom completely slipped off from the base of the penis during withdrawal from the vagina.
4. Condom completely slipped off from the base of the penis during withdrawal from the vagina due to not holding on to the base of the condom during withdrawal from the vagina.
5. A logical discrepancy arises between the individual parameters queried for clinical failure and the simultaneous exclusion of a clinical failure. In this case, the worst-case scenario is assumed, which implies a clinical failure of the condom.
6. The study objective is IELT duration, not clinical failure. If this parameter is missing/not ticked, it can be assumed there is no breakage or slippage and the IELT is considered to be valid. No further imputation of the question is carried out.
7. The slippage is after intravaginal ejaculation so the IELT can be used.

[redacted]



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