INVESTIGATION PLAN

A Phase II Evaluation of the Performance and Acceptability of Two Polyurethane Male Condoms (Sagami Original 001™ and Sagami Original 002™) Compared to a Commercial Latex Condom (Trojan Thintensity™) (Breakage/Slippage)

Protocol Number ***SAGCS 2***
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Prepared by Essential Access Health to meet the specifications of Sagami Rubber Industries Co., Ltd.

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I. Introduction

Although latex condoms have long been available as contraceptive devices as well as a means for preventing the spread of sexually transmitted infections, they remain the only reversible method of contraception for men and an effective means of preventing STI's including the transmission of human immunodeficiency virus (HIV), which can progress to AIDS.

Polyurethane condoms are intended to prevent pregnancy, HIV/AIDS, and other sexually transmitted infections per the guidance document: *Labeling for Natural Rubber Latex Condoms Classified Under 21 CFR 884.5300 - Class II Special Controls Guidance for Industry and FDA Staff.* Although polyurethane condoms are outside the scope of this guidance document the general requirements for natural rubber latex condoms apply equally to polyurethane condoms.

Currently available non-latex condoms are not as widely known or used as latex condoms by many consumers who seek products for price, thinness, dependability, comfort, and attractiveness. Limitations of latex condoms include their ability to maintain performance while becoming thinner, sensitivity, as well as their potential to induce allergy. Up to 3% of the U.S. population may be unable to use latex products for this latter reason.

The development of non-latex condom options offering thinner properties while maintaining performance and protection from sexually transmitted infection (STI) and pregnancy constitutes a major contribution to public health. These new thinner polyurethane products are non-latex (non-protein) allergenic, capable of withstanding environmental extremes and with performance, sensation and aesthetic characteristics appealing to condom users

Non-latex condoms are the biggest single advancement in condom contraception and STI protection since condoms were first developed. Of importance is the nature of non-latex polyurethane condoms as they are latex allergy free and the material can be thinner, smoother, increase heat transfer, odorless, and have a natural appearance. Condoms made of polyurethane provide both burst and tensile properties that comfortably meet the natural rubber latex condom minimum standard requirements. Polyurethane condoms can help encourage condom use and thus reduce unwanted pregnancy and lessen the transmission of STI's. This study may therefore benefit millions of people.

Sagami Rubber Industries, the manufacturer of the condoms, has been manufacturing condoms since 1934 and polyurethane condoms since 1990. Sagami polyurethane condoms are available in most countries throughout the world and the test condoms are currently marketed in Japan and throughout Asia demonstrating years of safe use of the product.

The primary objective of this study is to evaluate the breakage, slippage and acceptability of two test polyurethane male condoms of different thicknesses and size (0.024mm/58mm/190mm – SAGCS-A and 0.018mm/55mm/170mm – SAGCS-B) compared to a control commercial natural rubber latex male condom (Trojan Thintensity™ – 0.055mm/53mm/195mm - SAGCS-C). Acceptability will be evaluated by comparing physical attributes of the polyurethane and latex condoms, as well as perceptions about purchasing and using the products and condoms in general. The study will be conducted in accordance with ISO 29943-1:2017.

The Statistical Analysis Plan in Section VI. includes details of the methods of analysis that will be used. The primary effectiveness endpoint of the study is to confirm noninferiority with respect to total clinical failure rates (combined breakage and slippage) of two test polyurethane male condoms against a control latex condom. Each of the two test polyurethane male condoms will be compared independently against the control latex condom. A non-inferiority margin for the difference between the test condom total failure rate – the control natural rubber latex male condom total failure rate of 2.5% as specified in ISO 23409:2011 will be used to assess the results.

Test polyurethane condom SAGCS-A will be considered non-inferior to the control latex condom if a formal test of inferiority is rejected. Separately, test polyurethane condom SAGCS-B will be considered non-inferior to the control condom if a formal test of inferiority is rejected. Hence, one or both test condoms may be declared non-inferior based on the results of this three-arm functionality study. The study will be considered successful if either one or both of the test polyurethane condoms complies with the primary effectiveness endpoint.

II. Protocol

Summary

This investigation will enroll 300 heterosexual couples to use five test polyurethane male condoms SAGCS A (0.024mm/58mm/190mm), five test polyurethane male condoms SAGCS B (0.018mm/55mm/ 170mm), and five commercial control natural rubber latex male condoms SAGCS C (Trojan Thintensity™- 0.055mm/53mm/195mm). Both test polyurethane condoms and the control natural rubber latex condom are lubricated with a silicone lubricant. Couples will be randomly assigned to the sequence of use of condom type. We estimate that this assignment pattern will yield over 1,000 evaluable uses out of 1,500 potential uses of each of the three study condom types. The study will compare the acceptability and functional performance (breakage and slippage) of the two test polyurethane condom types to that of the control natural rubber latex male condom through interviews and questionnaires with subjects. The study will be conducted in accordance with ISO 29943-1:2017.

Selection Criteria

Both partners, based on self-report, should meet the following selection criteria:

Inclusion Criteria:

a. Between the ages of 18 and 45 (inclusive)
b. Protected against pregnancy by oral contraceptives, an IUD, an implant, contraceptive injections, contraceptive patch, or sterilization (tubal ligation or vasectomy)
c. Have home internet access, a valid personal email for each partner, ability to videoconference and use electronic signature technology
d. Willing and able to give electronic informed consent

e. Willing to respond to questions concerning their reproductive and contraceptive history and use of condoms via interview or self-administered questionnaires
f. Have vaginal intercourse at least once weekly
g. Willing to use the study products for fifteen acts of vaginal intercourse within nine weeks of study entry
h. In a mutually exclusive monogamous relationship with their study partner for at least 6 months and be willing to remain mutually monogamous throughout study participation
i. Both study partners have previous experience using male condoms
j. Agree not to use any additional vaginal or sexual lubricant except the Astroglide™ product provided, if desired, supplied by the study
k. Agree not to expose the study condoms to jewelry (hand, facial, or genital) or piercings (facial or genital) that could damage the study condoms.
l. Agree not to use sex toys or drugs intended to enhance or diminish sexual response when using study condoms
m. Male partner agrees to ejaculate during vaginal intercourse
n. Agree to (or partner) hold the condom at the base of the erect penis during withdrawal
o. Agree to return any condoms that break during use
p. Agree to return any unopened condoms
q. Reachable by telephone

Exclusion Criteria:

a. Currently participating in another similar clinical study
b. Female partner self-reported as pregnant
c. Allergic to natural rubber latex or polyurethane, or has a history of recurrent adverse events following use of latex or polyurethane products
d. Unable to follow study requirements, use instructions or attend study visits or exchanges
e. Have a significant (high) risk of STIs, including HIV infection, or having a medical history of recurrent, uncontrolled STIs (e.g. gonorrhoea, syphilis, Chlamydia, etc.)
f. Currently using condoms for protection against a known STI
g. Taking any internally applied medication to treat a genital condition that could interact with the study condom
h. Male partner has used medication that has caused erectile dysfunction, or had difficulty achieving/maintaining an erection, or achieving ejaculation in the last month under typical circumstances/conditions
i. Male has had a prostatectomy
j. Any self-reported genitourinary condition (e.g. itching, burning, irritation, etc.) which, in the opinion of the investigator, could affect use of the study condoms or the ability to interpret study data
k. Employee or affiliate of Essential Access Health or Sagami Rubber Industries Co., Ltd.

Procedures

Impact of COVID-19

A novel virus known as "SARS-CoV-2" causing the respiratory disease "Coronavirus Disease 2019" (COVID-19) was discovered in December 2019. In response to the outbreak of COVID-19,

the U.S. Department of Health and Human Services (HHS) declared a public health emergency on January 31, 2020 under section 319 of the Public Health Service Act (42 U.S.C. 247d). On March 13, 2020, the President of the United States issued a proclamation declaring a national emergency due to COVID-19.

As the COVID-19 public health emergency is still ongoing, study procedures will follow state and local policy for COVID-19 infection control. Study procedures will aim to protect trial participants Study Staff and reduce risk of viral transmission by:

1. *Decreasing proximity:* Remote visits will be conducted via videoconference or telephone where possible. Research staff will follow institutional SOPs governing privacy and security while conducing videoconference visits. Curbside exchanges will be conducted where social (physical) distancing of at least 6 feet is followed.
2. *Decreasing duration:* Curbside exchanges will be limited to the minimum amount of time necessary to complete study assessments. Further follow-up may be conducted remotely via videoconference or telephone.
3. *Decreasing confined spaces:* Curbside exchanges will be conducted in safe outdoor areas allowing for proper air circulation. In the event that a Curbside exchange cannot be completed outdoors (e.g. severe weather), the exchange can occur in a well-ventilated indoor space (other than the couple's) home where social distancing of at least 6 feet can be maintained . The indoor exchange will be completed in less than 15 minutes, if possible, while observing all other masking and infection control practices.
4. *Implementing masks and other infection control practices for study staff and participants:* Masks will be worn by research staff for the duration of any Curbside exchange, subjects will be instructed to wear masks, hand hygiene (use of alcohol-based hand sanitizer or hand-washing with soap and water) will be completed before and after the exchange, and shared work surfaces (clipboards, pens, tables, chairs, etc.) will be cleaned and disinfected before and after the exchange.

Recruitment

Study staff will read the study script and answer the questions of callers responding to the study recruitment campaign (outreach to former EAH study participants, Craigslist, social media, Google). Study staff will administer a pre-screening IRB approved set of questions to determine whether the caller and his/her partner is likely to be eligible for the study. If initially eligible, the caller will be emailed a copy of the informed consent to review. After the caller and his/her partner read the informed consent, the caller will phone the study to schedule a remote consent visit (SV1). Subjects will not sign the informed consent until that visit.

Consent/Instruction (SV1)

The consent visit (SV1) 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. Research staff will show company issued photo identification. Couples will receive information about the study and each partner will receive an electronic informed consent. Each couple will complete informed consent procedures, including electronically signing an informed consent form, prior to completing any study procedures. The original signed informed consent will also be signed by the research staff member conducting the

consent visit and an electronic copy of the signed consent will be provided to each subject. The fully signed informed consent will be kept on file by the investigator.

If for any reason it is not possible to sign the consent forms electronically, a facsimile or photographic image of the signed form may be sent through electronic means providing all other conditions of the Protocol are met. Alternatively, the signed consent form may be scanned and returned through a specified e-mail account, or posted to a specified internet address. Study subjects may bring the signed and dated consent form to the clinical site or Curbside meeting location, if restrictions on traveling to the Clinical Study site are alleviated, or send it to the clinical investigator by trackable/signed receipt mail. No study procedures may be conducted until the signed consent form is received, has been signed by the research staff member who conducted the consent visit, and a copy of the signed form has been provided to the subject.

After signing the informed consent, both partners will view a video which will demonstrate the correct way to don (teat up position) and remove condoms. 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 video and research staff will help to clarify any unclear directions. Research staff will instruct couples on how to take penis measurements using a penis measurement kit. Intensive instruction will also be given on completing all self-administered data collection forms.

Screening (SP-M, SP-F)

After the consent visit, each subject will separately complete a private remote screening via telephone without the other partner present. There will be a separate male phone screening (SP-M) and female screening visit (SP-F). At each visit, information on demographics and previous sexual, contraceptive, social, reproductive and medical history will be obtained. The screening visit will be used to assess the couple's eligibility. Subjects must meet all inclusion criteria and no exclusion criteria to be able to move onto the next part of the study and enroll.

Enrollment (E1)

If both partners are eligible after their screening, they will be invited to attend a Curbside exchange (E1) at which they will be enrolled into the study. This exchange will allow research personnel to meet the couple at a prearranged location (e.g. outdoor office space, clinic parking lot, etc.) that is safe for the participants and study staff to exchange study supplies and data. For subjects who are able to drive to the meeting site, subjects will stay in their car while research staff complete exchange procedures outside. Alternatively, research staff may meet the couple at their residence or other prearranged location and conduct the exchange at a sufficient distance (such as on their doorstep). If the exchange is conducted at a subject's residence, research staff must stay outside and not enter the home.

At enrollment (E1), both partners must be present with a valid, official government-issued photo identification to re-verify their identity before they can be enrolled and receive investigational product. The couple will receive their initial set of study supplies, including a penis measurement kit, five condoms of their first randomly assigned type of study condom, five condom reports, one

acceptability questionnaire for each partner and a supply of at least 4 oz. of Astroglide™ study lubricant to use if desired during their study participation. The couple will also receive five small sealable plastic pouches and one larger black plastic sealable plastic pouch for any condoms that break or tear. Each broken or torn condom should be sealed in an individual small pouch and the small pouch(es) should be placed inside the larger pouch. Any claimed broken or torn condoms should be returned double-bagged at the next Curbside exchange.

If a couple does not keep their scheduled enrollment, no further attempts will be made to contact the subjects.

Follow-Up (E2, E3, E4)

There will be three follow-up Curbside exchanges (E2, E3 and E4). Only one partner will be required to be present at each Curbside exchange.

E2 will be scheduled within three weeks of the enrollment. At E2, participants will return their completed condom reports and acceptability questionnaires. They will also return any unopened condoms and claimed broken or torn condoms. Used condoms should be returned double-bagged. Study staff may review reports and questionnaires for any missing or unclear responses. Simple clarifications that can maintain confidentiality and physical distance can be done Curbside. Further clarifications and follow-up will be completed remotely via telephone or video. Research staff will distribute five condoms of their next randomly assigned type of condom, five condom reports and one acceptability questionnaire for each partner. Additional lubricant will be supplied as needed at each exchange. The couple will also receive five small sealable plastic pouches and one larger black plastic sealable plastic pouch to double-bag any claimed broken or torn condoms. Each broken or torn condom should be sealed in an individual small pouch and the small pouch(es) should be placed inside the larger pouch. Any claimed broken or torn condoms should be returned double-bagged at the next exchange.

E3 will be scheduled within three weeks of the prior follow-up exchange. In addition to the procedures conducted during E2, a comparison form for each partner will also be distributed at E3.

E4 will be scheduled approximately three weeks after the prior follow-up exchange. At this exchange, participants will return their completed condom reports, acceptability questionnaires and comparison forms. They will also return any unopened condoms and claimed broken or torn condoms. Used condoms should be returned double-bagged. Study staff may review reports and questionnaires for any missing or unclear responses. Simple clarifications that can maintain confidentiality and physical distance can be done Curbside. Further clarifications and follow-up will be completed remotely via telephone or video.

If a couple does not keep their scheduled follow-up Curbside exchange, research personnel will initiate a reminder contact and reschedule the exchange.

In the event that state and/or local authorities issue social distancing guidelines that do not allow for Curbside exchanges, investigational product and study materials may be delivered to study subjects via expedited, traceable mail service if allowed by current FDA guidance and with

advance permission from the sponsor. Similarly, subjects who are unable to complete a Curbside exchange due to safety concerns, particularly due to risk of COVID-19 transmission, may have their study supplies shipped with approval from the sponsor. A traceable, pre-paid return envelope will also be provided with instructions for the subject to return completed reports, questionnaires, forms and unopened, torn or broken condoms. Used condoms must be returned double-bagged. Subjects will be instructed to confirm with the study staff when they receive their package and when they ship their return package. Upon receipt of study materials, study staff will review the forms and clarify any missing or unclear responses with the subject via telephone or video.

Neither partner will be examined physically unless the partner reports a persisting adverse reaction (irritation, rash, burning, abnormal vaginal discharge, etc.) which arises during their study participation. Clinical examinations will be arranged if the adverse event has not already resolved. The clinical examination of female participants will consist of a pelvic examination including description of external genitalia, vagina, and cervix. Additional tests such as a vaginal wet mount or vaginal swab may be completed as needed. The clinical examination of male participants will consist of an andrology examination including appearance of skin of penis and scrotum, presence or absence of circumcision, position of urethral meatus, size, position, shape and consistency of testes, epididymis, vas and cord.

Couples will be permitted to have vaginal intercourse as desired during the study provided this does not affect their ability to use the study condoms within the stipulated timeframe.

Exit (XP)

An exit visit (XP) will be conducted via telephone. The exit (XP) should be done as soon as possible after the fourth follow-up exchange (E4) or within approximately two weeks after the prior visit. Research staff will conduct a final review of all study forms and materials and clarify any missing or unclear responses with the subject. This will complete study participation for the couple.

Early Discontinuation (ED)

A couple will be considered an early discontinuation if they stop their study participation before completing the final follow-up Curbside exchange (E4) and exit visit (XP). Couples can withdraw from the study at any point. If a couple decides to discontinue their participation in the study (e.g. withdraw consent due to personal circumstance, adverse event, etc.) or is discontinued from the study for any other reason (e.g. lost to follow-up, non-compliance, etc.), the reason for early discontinuation should be documented and the couple will be instructed to complete the final follow-up Curbside exchange (E4) and exit visit (XP).

If the subject is unable to attend the final Curbside exchange (E4) and exit visit (XP), study staff will send each partner an exit package via a traceable delivery service. The package will include a traceable, pre-paid return envelope with instructions for the subject to return completed reports, questionnaires, forms and unopened, torn or broken condoms. Used condoms must be returned double-bagged. Subjects will be instructed to confirm with the study staff when they receive their package and when they ship their return package. Upon receipt of study materials, study staff will

review the forms and clarify any missing or unclear responses with the subject via telephone or video.

Lost to Follow-up

If a couple does not keep their scheduled enrollment (E1), no further attempts will be made to contact the subject and they will be declared lost to follow-up.

For all enrolled couples who fail to attend a scheduled Curbside exchange or respond to study staff attempts to reschedule the exchange, study staff will make ongoing attempts to contact both partners until the study is over or until one or both partners withdraw consent. If study staff are unable to re-establish contact through phone, email, or text message, study staff will send each partner an exit package via a traceable delivery service instructing the subject to contact research staff within weeks of receipt of letter. The package will contain a traceable, pre-paid return envelope in which to return completed reports, questionnaires, forms and unopened, torn or broken condoms. Used condoms must be returned double-bagged. Research staff must also call any back-up contacts on record for the couple. If the both partners remain unresponsive at the end of the study, the couple will be declared lost to follow-up.

Data Collection

At the male and female phone screenings (SP-M and SP-F), an initial history will be obtained. The history will elicit information on previous condom use, sexual partners, coital patterns, history of STIs, vaginal infections, and disorders of the reproductive system.

At the first Curbside enrollment visit (E1), couples will be given a penis measurement kit and asked to take measurements of the male's erect penis (length and circumference) prior to use of the first study condom.

At every follow-up Curbside exchange (E2, E3, and E4), each couple will be asked to return a completed condom report for each use of a study condom within 30 minutes after ejaculation. These reports will elicit information on the conditions of use (who put on condom, use of lubrication, duration of vaginal intercourse, positions used during intercourse), subjective impression (ease of donning, fit, quality of lubrication), whether the condom was held at the base of the erect penis during withdrawal, and problems encountered (breakage, slippage, discomfort, lack of lubrication), circumstances of problems encountered (e.g. when noticed, duration). Written instructions and definitions/illustrations of potential condom problems such as breakage and slippage will be attached to the condom report forms.

After completing each set of five condoms, partners will complete acceptability questionnaires regarding their overall experience with each type of condom and return the questionnaires at the next follow-up Curbside exchange (E2, E3, and E4). These self-administered questionnaires, completed independently by both partners, will elicit perceived advantages, disadvantages, problems, and physical reactions related to condom use.

At the fourth and final Curbside exchange (E4), each partner will return a completed comparison form that elicits preferences between the two types of test polyurethane male condoms regarding sensation, comfort, lubrication, fit, ease of use, overall preference, etc.

Data coding, editing, and key entry will be performed at Essential Access Health. Entrypoint Plus software will be used to structure and maintain data files. Raw data from this study will be made available to the Sponsor as MS Excel files.

Length of Study Participation/Study Timeline

The start-up phase of this investigation will be limited to four weeks. The initiation of advertising/ recruitment and the preparation/duplication of data collection instruments will be accomplished during this phase.

It is estimated that approximately 20 couples will be enrolled each week requiring a recruitment/ enrollment phase of 15 weeks to achieve a sample size of 300 couples. A follow-up phase of 11 weeks should allow the last enrollments to complete their participation. Couples are expected to complete their study participation within nine weeks of entering the study. Eight weeks will be dedicated to analysis and report writing after completion of subject follow-up.

Management of Claimed Broken or Torn Condoms

Claimed broken or torn condoms will be shipped to Sagami Rubber Industries Co., Ltd. (Kanagawa-ken, Japan) in bulk shipments. Condoms will be shipped in the double sealed plastic pouches provided to study subjects, encased in a single large sealable plastic bag, and placed in heavy duty cardboard shipping boxes.

III. Subject Compensation

Each partner will be reimbursed with a $150 ($300 per couple) via a cash card at the exit phone visit (XP) for time and transportation costs associated with completing the consent visit (SV1), their SP-M or SP-F, four follow-up exchanges (E1, E2, E3, E4), a phone exit (XP), using 15 study condoms and completing 15 condom reports. If couples do not complete the study, they will be paid according to the number of visits/exchanges they attended, the number of study condoms they used, and the number of condom reports they completed.

IV. Institutional Review and Informed Consent Procedures

Prior to enrolling study subjects, the study will be reviewed and approved by the Institutional Review Board (IRB) in accordance with FDA regulations (21 CFR Part 50, 21 CFR Part 56 and 21 CFR Part 812). A copy of the IRB approval letter and the IRB approved consent form will be sent to the sponsor. The sponsor, Essential Access Health and IRB will approve all revisions and/or amendments to the protocol in advance in writing. If required, these will be filed with the U.S. Food and Drug Administration.

Protocol violations will be reported to the sponsor, Essential Access Health and IRB in accordance with IRB requirements.

Informed Consent Procedure

After phone pre-screening, subjects will be emailed a copy of the informed consent to read prior to their consent visit and will be instructed not to sign the form. At the consent visit, the purpose and requirements of the study will be explained before prospective subjects are presented with an electronic informed consent form identical to the one provided prior to the visit. Subjects will also be advised that more detailed information about sexual activity will be collected than is typical of most family planning visits. Subjects will be given an opportunity to ask questions about the study condoms and/or the content of the informed consent. Subjects will be informed that their partners must also agree to participate in the study in order for them to join. If both members of the couple agree to participate, they will each electronically sign the informed consent form using Part 11 compliant software. The consent form will also be signed by the research staff member conducting the consent visit. The consent form will include each of the basic and additional elements of informed consent described in 21 CFR Part 50. All subjects will be required to provide a signed informed consent before they are enrolled in the study and will receive a copy of their fully signed informed consent form.

V. Study Design

This study is a masked (investigators, research staff), three-arm crossover, randomized to sequence of use study designed to evaluate the functional performance (breakage, slippage) of two test polyurethane male condoms (.024mm/58mm/190mm – SAGCS-A, .018mm/55mm/170mm – SAGCS-B) each compared to a commercial natural latex condom. (.055mm/53mm/195mm - Trojan Thintensity™ – SAGCS-C). All three study condoms are lubricated with a silicone lubricant. Three hundred (300) couples will be enrolled and asked to use five condoms of each of the study condom type to yield a potential sample size of 1,500 uses for each type of lubricated condom. To minimize a potential learning effect, couples will be randomly assigned to one of six possible sequences of use of the study condoms:

- SAGCS-A – SAGCS-B – SAGCS-C
- SAGCS-A – SAGCS-C – SAGCS-B
- SAGCS-B – SAGCS-A – SAGCS-C
- SAGCS-B – SAGCS-C – SAGCS-A
- SAGCS-C – SAGCS-A – SAGCS-B
- SAGCS-C – SAGCS-B – SAGCS-A

From experience with previous condom breakage/slippage studies, we estimate that at least 85% of couples will complete all 15 condom uses to obtain an actual sample size of approximately 1,275 for each condom type.

The primary effectiveness endpoint of the study is to confirm noninferiority with respect to total clinical failure rates (combined breakage and slippage) of the two test male condoms independently against the control natural rubber latex male condom. As specified in ISO 23409:2011 a noninferiority margin, δ, of 2.5% will be used.

VI. Statistical Analysis Plan

Sample Size Justification

The power calculations to determine the minimum number of couples and condom uses will be done using the formula given in annex A of ISO 29943-1:2017 adjusted for a one-sided confidence level of 97.5%. The formula for sample size is:

$N = \{G(P) + 1.960\}2 \times Var(\Delta) / \{(\delta - \Delta)^2\}$

where

$Var(\Delta) = Pt(1- Pt) \times \{1+(Z-1)\ \rho\}/Z + Pc(1- Pc) \times \{1+(Z-1)\ \rho\}\ /Z - 2\ \rho \times \{\ Pt(1- Pt) \times Pc(1- Pc)\}^{1/2}$

and $G(P)$ is the inverse cumulative normal probability function for the specified power P, Pt and Pe are the true (unknown) total clinical failure probabilities for the test and control natural rubber latex male condoms respectively, ρ is the level of within couple correlation for failure rate, Z is the number of condoms per type used and $\Delta = Pt - Pc$.

A correlation factor of 0.2 for the within couple total clinical failure rate between the test polyurethane and control natural rubber latex male condoms, and an upper limit of 4% combined failure rate, and a minimum power of 90% will be used for the sample size calculations. Assuming 85% of condom uses meet inclusion criteria (1,275 condom uses), the statistical power is estimated at 95% according to the method of calculation given in Annex A of ISO 29943-1: 2017.

Statistical Objectives

The primary effectiveness endpoint of the study is to confirm noninferiority with respect to total clinical failure rates (combined breakage and slippage) of two test polyurethane male condoms against a control natural rubber latex male condom. Each of the two test polyurethane male condoms will be compared independently against the control natural rubber latex male condom. A non-inferiority margin, for expected test condom total failure rate – expected control natural rubber latex male condom total failure rate of 2.5% as specified in ISO 23409:2011 will be used to assess the results. This three-arm functionality study with two test polyurethane male condoms and one control natural rubber latex male condom will be conducted in accordance with ISO 29943-1:2017.

Each test polyurethane male condom will be assessed independently against the control natural rubber latex male condom. For each comparison, the study hypotheses will be:

> Null Hypothesis, H0: Expected test condom total clinical failure rate – expected control natural rubber latex male condom total clinical failure rate ≥ δ, where δ = 2.5%;
>
> Alternative Hypothesis, HA: Expected test condom total clinical failure rate – expected control natural rubber latex male condom total clinical failure rate < δ, where δ = 2.5%;

For each of the comparisons (i.e., each of the two test condoms versus control condom), if the null hypothesis of inferiority is rejected using an appropriate test statistic, then the alternate hypothesis of non-inferiority will be accepted. Based on this set of co-primary hypotheses, either or both test condoms may be declared non-inferior to the control condom.

We will use the Bonferroni correction to adjust the power for the three-arm study. As a consequence, one-sided upper limits of the 97.5% confidence intervals rather than 95% confidence intervals specified in the FDA guidance document and ISO 23409:2011 will be used to assess whether the non-inferiority hypotheses using a non-inferiority margin of 2.5% are accepted or rejected. To meet the noninferiority requirement the upper 97.5% bound of the one-sided 97.5% confidence interval, *U*, shall be equal to or less than 2.5%, i.e.

$$U = \left(\hat{P}e - \hat{P}c\right) + 1.960\,SE$$

where $\left(\hat{P}e - \hat{P}c\right)$ is the estimated difference in total clinical failure rates between the test and control latex condoms and *SE* is the standard error of the difference (Taylor [1]).

Taylor (ibid) provides a simple formula for estimating the standard error for paired differences in observed failure rates among study couples. This method, however, requires all couples to provide data for both condom types and does not allow for within couple correlation of failure rates (clustering). To overcome these limitations the method of Generalized Estimating Equations (GEE) will be used to estimate the regression parameters and their standard errors (Diggle et al [2], Taylor and Dominik [3]).

The primary effectiveness of the condoms will be analysed by GEE separately for each of the two polyurethane test condoms against the common control natural rubber latex male condom using the PROC GEE procedure in SAS (or R if SAS is not available to the analyst) with an identify link function and an independent working correlation structure to calculate the limits of the one-sided upper 97.5% confidence intervals for the difference in the total clinical failure rates for the test polyurethane male condoms minus the control natural rubber latex male condom.

For each separate primary analysis, couples will need to have reported use of at least one test polyurethane male condom and one control natural rubber latex male condom for vaginal intercourse. Non-use of 5 condoms of each type will assumed to be non-informative for this primary analysis We will report the amount of missing data per condom type; explore possible confounding due to differential missing data by type; and perform a sensitivity analysis based on 'completers' (i.e., use of all 5 condoms of each type being compared). For analysis purposes missing outcome data for individual condom uses will be assumed to be missing completely at random. The potential for informative cluster sizes and resulting bias (e.g. if couples with higher

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[1] Taylor, Issues in the design, analysis and interpretation of condom functionality studies, Contraception 80 (2009) 237 - 244

[2] Diggle, Heagerty, Laing and Zeger, Analysis of longitudinal data, 2nd ed. Oxford University Press; 2002

[3] Taylor and Dominik. Noninferiority testing and crossover trials with correlated binary outcomes and small event proportions with applications for the analysis of condom failure data, J Biopharm Statistics, 9 (2) 365 – 377 (1999)

failure probabilities use fewer condoms of either condom type) will be explored to the extent possible in sensitivity analyses. We will also assess the reasons for missing data by condom type in order to examine the assumption of randomness of missing data.

The power calculation used to determine the sample size is based on the assumption that 85% of condom uses will meet the inclusion criteria (1,275 condom uses). The 85% assumption is based on past experience of running studies of this nature. The use of a high initial power target of 95% for the calculations provides a significant level of protection against the consequences of higher than expected discontinuation rates with resulting loss of missing primary effectiveness data. If the completion rate drops to 75%, power will still exceed 90%. Even if the completion rate drops to a low as 60% the power to conclude noninferiority will remain marginally higher than 80%.

Definition of the primary effectiveness endpoint, total clinical condom failure rate:

The probability of total clinical condom failure is defined as the number of condoms that break or slip completely off the penis during intercourse or correct withdrawal as a proportion of the condoms used for vaginal intercourse.

Observations contributing to the analyses

Condoms used for vaginal intercourse will be included in the analysis with the following exceptions:

1. Condoms used for anal intercourse during the same act.
2. Condoms used during oral sex during the same act.
3. Condoms exposed to mouth or genital jewelry.
4. Condoms used other than with the supplied Astroglide™ lubricant.
5. Condom packages opened with sharp objects or teeth.
6. Condoms that slipped completely off the penis when not held at the base of the erect penis during withdrawal

Additional Analyses

Functionality measures (including measure that will be included in the primary effectiveness endpoint of total clinical failure)

The analysis will include the calculation of the following functionality measures for both condom types. These will be reported as probabilities including 95% confidence intervals.

Nonclinical failure:	Number of condoms that could not be used because of breaks, donning problems, or defect over the number of condoms opened for use
Clinical breakage:	Number of condoms that broke during intercourse over

	the number of condoms used for vaginal intercourse (clinical breakage will be included in the primary effectiveness endpoint of total clinical failure)
Complete slippage	Number of condoms that slipped completely (100%) off the erect penis during intercourse or on correct withdrawal over the number of condoms used for vaginal intercourse. (Condoms that slip completely (100%) off the penis during withdrawal when neither partner held the condom at the base of the erect penis during withdrawal are excluded.)
Slippage during intercourse:	Number of condoms that slipped off penis during intercourse over the number of condoms used for vaginal intercourse
Slippage during withdrawal:	Number of condoms that slipped off penis during withdrawal over the number of condoms used for vaginal intercourse.
Partial slippage:	Number of condoms that slipped off penis during withdrawal over the number of condoms used for vaginal intercourse.
Total failure:	Number of condoms that broke during package opening, donning, intercourse or correct withdrawal, or slipped off the penis during intercourse or correct withdrawal or could not be used (donning problems or defect) over the number of condoms opened for use.
Total slippage:	Number of condoms that slipped off penis during intercourse or correct withdrawal over the number of condoms opened for use (total slippage will be included in the primary effectiveness endpoint of total clinical failure)
Other failure:	Number of condoms that could not be used due to donning problems or defect over the number of condoms opened for use

We will also assess the association between penis size and breakage/slippage for each condom type e.g., whether increased or decreased rates for total clinical failure, clinical breakage and total slippage as a function of penis size.

Acceptability measures

Acceptability will be evaluated by comparing physical attributes of the three condom types as well as perceptions about using the product. The following acceptability and preference information will be collected for the three types of condoms:

a. fit of condom (comfort, lack of movement, lack of constriction)
b. ease of donning

c. removing
d. sensitivity/pleasure (heat transmission, speed of orgasm)
e. adequacy of lubrication
f. noise during use
g. appearance
h. condom smell/odour
i. overall preference (liked best/least)
j. recommend to others
k. purchase interest/acceptable price

Each partner will rate condom attributes on a scale from 1 to 7. Ordinal acceptability data will be summarized by gender with a mean score for each condom type. Paired t-tests (Alpha= 0.05) will be performed to determine whether the acceptability measures are statistically different. Chi-square tests (Yates correction will be applied when cell sizes contain less than ten events) will be performed for categorical acceptability data. Preference data, including the level of confidence the participants have in the condom type just used, the attribute liked best, the attribute liked least, and their willingness to purchase and recommend the condom type to a friend, will also be summarized.

We will also report genital discomforts and adverse events probably or possibly related to the use of each condom type (see below for definitions of genital discomforts and adverse events).

Baseline and Other Summary Data

Sociodemographic characteristics, as well as information from the reproductive and contraceptive histories will be presented by gender. Other events, behaviours, and use details (use of lubricants, ease of insertion, etc.) associated with the use of the study condoms will be presented by condom type.

VII. Risk Analysis

Potential Risks

The study does not involve any procedures associated with significant risk. Couples at risk of pregnancy or at significant (high) risk of sexually transmitted infection are excluded from study participation. Minor side effects related to condom and lubricant use may include irritation, rash, itching, swelling and redness of the genitalia. These side effects are expected to be self-limiting.

Protection of Subjects

Detailed verbal and written instructions on correct condom use will be provided to all participants. Subjects will be instructed to contact research staff immediately if they encounter any problems related to the study or any major medical problem. Serious adverse events will be reported as soon as possible but no longer than 10 days to the sponsor and will be reported to the IRB in accordance with IRB requirements.

To assure subject confidentiality, subject names will not appear on study data forms. All data records will be identified by study ID number and may contain either initials or date of birth. Data records will not contain any other identifiers such as name, social security number, or address. Participants will be advised that any information they give will not be shared with their partner except at their specific request.

Potential Benefits

There are no direct benefits to subjects associated with study participation. The results of this study may benefit others in the future by making more contraceptive methods available.

Evaluation of Risks and Benefits

As discussed above, there are no known serious risks or substantial benefits associated with study participation.

VIII. Description of Study Population

Monogamous couples protected against pregnancy by oral contraceptives, an IUD, contraceptive injections, contraceptive patch, or sterilization (tubal ligation or vasectomy) will be recruited via social media (Facebook), on-line advertising (Google), Internet classifieds (Craigslist, college newspapers), and from a database of previous study subjects to assure a diverse, representative study population. Couples will have had previous condom experience.

IX. Description of Devices

The condoms used are described as follows:

	Test Condom I SAGCS-A	Test Condom 2 SAGCS-B	Control Natural Rubber Latex Male Condom* SAGCS-C
Commercial Name	Sagami Original 002 (24) ™	Sagami Original 001 (18) ™	Trojan Thintensity ™
Condom Type	Polyurethane	Polyurethane	Natural Latex
Nominal Length (mm)	190 +/-10	170 +/-10	195 +/-10
Nominal Flat width (mm)	58 +/-2	55 +/- 2	53 +/- 2
Nominal Thickness, mid-length (mm)	0.024 +/- 0.008	0.018mm +/- 0.008	0.055mm +/- 0.010
Lubricant type (cSt)	Silicone Oil 100	Silicone Oil 100	Silicone Oil 100
Lubricant quantity (g/pc)	0.40 – 0.60	0.40 - 0.60	0.40 – 0.60
Appearance	Cylindrical, with reservoir tip	Cylindrical, with reservoir tip	Cylindrical, with reservoir tip

*Marketed, sold and distributed in the USA by Church & Dwight.

The test polyurethane and control natural rubber latex male condoms will be packaged in foiled tub packages. A label with the study identification number (protocol number) and condom identification number (A, B, or C), will be applied to each individual condom package. In addition,

in accordance with 21CFR812.5, labelling will also include the statement: "CAUTION: Investigational Device. Limited by Federal (or United States) Law to Investigational Use." Essential Access research staff will not know condom assignment until all study data have been analysed and tabulated.

X. Adverse Event Management

Subjects will be instructed to contact research staff immediately if they encounter any problems related to the study or any major medical problem. For this study, an Adverse Event (AE) Form is completed for any of the following: 1) genitourinary discomfort reported on a condom report that lasts more than an hour, 2) a non-genitourinary medical problem that might be related to condom use, 3) a new genitourinary condition that starts after use of a study condom, or 4) a serious adverse event. AE Forms are not completed for discomfort/problems that are reported on the condom report and last for less than an hour. A serious adverse event is defined as an adverse experience or concomitant illness that results in death, life-threatening situation, permanent disability, hospitalization, or congenital anomaly. An unanticipated event is defined as one that is not identified in nature, severity, or frequency in the protocol or human safety assessment.

The Principal Investigator (PI) will promptly notify the sponsor by telephone or email of any serious adverse event whether or not related to use of the study condom, or of any unanticipated event that is possibly related to use of the study condom. Also, the PI will notify the Essential Access IRB of any such event as required by IRB policies.

A clinical examination will be arranged for any subject who reports a persistent adverse reaction (irritation, rash, burning, etc.) which arises during his/her study participation if the adverse reaction has not resolved prior to the report. In an acute medical situation, the randomization code will be broken if the PI deems this essential for medical management of the subject. The PI will notify the sponsor as soon as possible, preferably before breaking the code. If the code is broken, the time and reason will be documented for study record and a copy sent to the sponsor.

XI. Quality Assurance and Data Monitoring

The sponsor will conduct four study monitoring visits over the course of the study. The timing of these visits will be as follows: an initiation visit, two mid-study visits during enrollment and follow-up, and a study close-out visit.

XII. Additional Records and Reports

A final report will be prepared after data collection and analysis is complete. The report will contain tables that present descriptive statistics on the study population, study outcomes, and acceptability measures. Results of statistical tests will be included where appropriate. Narrative descriptions of all results and methods of analysis also will be included.

XIII. Management of Essential Access Health Northern California Office

Study data will be entered into the study database using 21 CFR Part 11 compliant EntryPoint Plus software. After data collection is completed, all Northern California source documents and

CRFs will be shipped via a traceable overnight carrier to the Essential Access Health Research Center in Los Angeles for long term storage. Scanned copies of all shipped documents will be maintained as electronic back-up.

The Sponsor will ship study product directly to the Essential Access Health Research Center in Los Angeles. Research staff in Los Angeles will randomize all study product and then ship randomized and masked study product to the Essential Access Health Northern California office via a traceable overnight carrier. Study Shipment Logs will document all shipments of study products between the Los Angeles and Northern California offices.