NCT05553600

Clinical Study Protocol

Protocol Title:	An Open-Label Clinical Validation Study of an Applicator Tampon
Protocol #:	AFC-21-001
Sponsor:	Kimberly-Clark Corporation
Protocol Date:	24 August 2022
Version:	2.0

[redacted]

SPONSOR PROTOCOL APPROVAL SIGNATURE PAGE

Protocol #: AFC-21-001

Title: An Open-Label Clinical Validation Study of an Applicator Tampon

Date: 24 August 2022

Version: 2.0

Reviewed and approved by the following Sponsor Representative:

[redacted]

Director, Global Medical Affairs

[redacted] Aug 26, 2022

Signature Date

INVESTIGATOR STATEMENT

An Open-Label Clinical Validation Study of an Applicator Tampon

I, the undersigned, have read this protocol and agree to conduct this protocol in accordance with ethical principles as outlined in the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements and any additional conditions mandated by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I acknowledge that I am responsible for the overall study conduct and I agree to personally conduct or supervise the described clinical study.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Kimberly-Clark Corporation.

_____	_____	_____
Principal Investigator Printed Name	PI Signature	Date

2 PROTOCOL SYNOPSIS

Protocol Title:	An Open-Label Clinical Validation Study of an Applicator Tampon
Protocol #:	AFC-21-001
Study Design:	This prospective multi-center, open-label, randomized, cross-over study is designed to validate that changes to the design of [redacted] tampons meet the following user needs: - product to remain clean prior to use, product to remain in working condition prior to use, to be able to access the product, to be able to vaginally insert and place the tampon, to be able to remove product from the vagina after use, product to absorb fluid, to be able to distinguish between absorbency levels, packaging to be labeled properly. Subjects will be assigned to one of two arms in the study: a regular absorbency arm or a super absorbency arm. Within each arm, a subset of 60 subjects will undergo gynecological exams prior to and following tampon use. Subjects will be randomly assigned the order in which to test a new tampon design (test tampon) and a currently marketed tampon (reference tampon). Each tampon type will be used over the course of one (1) menstrual cycle. Subjects will be provided with 16 tampons per menstrual cycle. For subjects undergoing gynecological exams, the study consists of 4 visits for each study subject, 2 visits for each menstrual cycle: one before and after each menstrual cycle. The first visit will be both the screening and the first pre-use visit. Pre-use visits will be conducted within 72 hours prior to expected menstruation. Post-use visits are to be completed within 72 hours following the last tampon use for that menstrual cycle. Subjects will undergo gynecological exams at each visit. Subjects will keep a daily diary during menstruation with entries for every tampon use. Subjects will also collect each used tampon to be returned to the clinical site for inspection by study staff to assess tampon integrity. Additionally, these subjects will complete an interview during the first visit to assess whether the subject can locate key information on the product packaging. For the remainder of the subjects, the study will consist of 3 visits for: a screening and pre-use visit, and two post-use visits. Post-use visits are to be completed within 72 hours following the last tampon use for that menstrual cycle. Subjects will keep a daily diary during menstruation with entries for every tampon use. Subjects will also collect each used tampon to be returned to the clinical site for inspection by study staff to assess tampon integrity.

Objective: The objective of this study is to validate that changes in the design of the [redacted] tampons meet defined user needs.

Endpoints:

Primary: The proportion of used tampons that have elongated will be used to assess the following user need:

- User can remove product from the vagina after use

Analysis will be done separately for each absorbency.

Key Secondary: Diary responses will be used to assess the following user needs:

- Product to remain clean prior to use
- Product to remain in working condition prior to use
- User can access the product
- User can vaginally insert and place the tampon
- User can remove product from the vagina after use
- Product absorbs fluid

Analysis will be done separately for each absorbency.

Interview responses will be used to assess the following user needs:

- User is able to distinguish between absorbency levels
- Packaging is labeled properly

Interview responses will be analyzed for both absorbencies combined.

Product tolerability will be evaluated through the following measures:

- Gynecological exam findings
- Frequency and severity of adverse events

Validation Criteria: The objective will have been met if the following criteria are met:

- The test tampon elongation rate is the same as or better than the reference tampon for each absorbency, where same is defined as test tampon elongation rate ≤ reference tampon elongation rate.
- Product tolerability is deemed to be acceptable based on review of the results.
- Diary responses have ≥ 96% response rates consistent with each user need for each absorbency. If the rate is lower than 96%, the response rate consistent with the user need related to the test tampon must be the same as or better than the response rate of the reference tampon, where same is defined as test tampon response rate ≥ reference tampon response rate.
- Interview responses demonstrate that 95% of users are able to identify key information on the package and insert, and

able to distinguish between absorbency levels on the wrappers.

Population:

The study population consists of 2 arms of approximately 369 females (total 738 subjects), ages 18-49, in good general health, in the United States who normally use tampons for menstrual protection, menstruate regularly, and do not have a history of Toxic Shock Syndrome (TSS). One arm will test regular absorbency tampons and the other will test super absorbency tampons. Within each of these arms, a subset of 60 subjects will undergo gynecological exams before and after product use.

Eligibility Criteria:

Inclusion Criteria

1. Willing and able to read and provide written informed consent.
2. Female in good general health, age 18-49 (inclusive).
3. Last pap smear was normal in the past 3 years, or a normal pap with a negative HPV in the past 5 years, or negative HPV in the last five years (age <21 does NOT need a PAP or HPV result) based on self-report
4. History of regular menstrual cycles during the previous 3 months lasting approximately 21-35 days, including at least 4 days of menstruation, and expecting to menstruate during the study period.
5. Tracks menstruation and able to confidently predict onset of menstruation within 72 hours.
6. History of use of applicator tampons without discomfort.
7. Normally use at least 6 tampons for protection during menstruation.
8. Normally uses regular, super, and/or super plus absorbency tampons for menstrual protection.
9. If uses super plus absorbency, must be willing to wear nothing greater than super absorbency for the duration of the study.
10. Agrees not to use douching substances, vaginal medications, suppositories, or vaginal devices for the duration of the study.
11. **[For subjects undergoing gynecological exams only]** Agrees not to apply feminine deodorant spray, powders, perfumes, wipes, lotions, creams, or emollients to the genital area for at least 24 hours prior to each visit.
12. Agrees not to try any new products in the vaginal/perineal area two (2) weeks prior to the study start and for the duration of the study.
13. Agrees to the conduct of all study procedures, including gynecological exams (if applicable), and agrees to follow all study instructions and return for scheduled appointments.
14. Has used an acceptable form of birth control for at least one month prior to enrollment and for the duration of the study. Acceptable methods include hormonal contraceptive, IUD,

tubal ligation, partner vasectomy, condom (with or without spermicide), or abstinence.

Exclusion Criteria

1. Pregnant, lactating or is trying to become pregnant.
2. Less than six (6) weeks post-partum.
3. Has a menstrual abnormality (such as oligomenorrhea or amenorrhea).
4. History of any of the following diagnoses based on self-report: diabetes, active genital herpes lesion in last 3 years, Human Immunodeficiency Virus (HIV), Pelvic Inflammatory Disease (PID), Toxic Shock Syndrome (TSS).
5. History of an abnormal pap smear within the last 3 years, positive HPV in the last 5 years, any form of gynecological cancer, or gynecological disorder such as fibroids, or endometriosis (by self-report). Participants that have had a history of an abnormal pap smear, but most recent pap smear has been normal, may be included.
6. Has a medical condition which might compromise her immune system functions (such as cancer, immunosuppressive therapy, anemia currently being treated under the care of a physician, leucopenia, HIV-positive, or organ transplant).
7. Has used steroid medications (systemic or topical) for fourteen (14) or more consecutive days within the last sixty (60) days.
8. **[For subjects undergoing gynecological exams only]** Has Type B (petechia, ecchymoses) or C (peeling, abrasions, ulcerations, or lacerations) lesions on the perineum, vulva, urethra, vagina, or cervix as determined by the investigator at the screening visit.
9. **[For subjects undergoing gynecological exams only]** Has Type A (erythema or edema) lesions covering >50% of any of the perineum, vulva, urethra, vagina, or cervical locations as determined by the investigator at the screening visit.
10. Has had clinically identified genital warts/lesions and/or urogenital infection (such as bacterial vaginosis, Trichomoniasis, yeast infection, Chlamydia trachomatis, Neisseria gonorrhea, or a urinary tract infection) within the past 6 weeks.
11. Has a known allergy or sensitivity to components of the investigational products, including rayon.
12. Any other medical condition or history, as determined by the Investigator that could compromise the study results or subject safety.

Planned Number of Sites: Up to 9 sites in the United States

Test Article(s):	• Modified [redacted] Tampons – Regular and Super Absorbencies (test tampons) • Commercial [redacted] Tampons – Regular and Super Absorbencies (reference tampons)
Anticipated Study Duration:	Approximately 6 months
Participant Duration:	Approximately 2 months

Table 1 - Proposed Schedule of Events

Event	Visit 1 Screening/Baseline	Visit 2 Post-Use Visit	Visit 3 Pre-Use Visit	Visit 4 Post-Use Visit	Unscheduled Visit
Informed Consent	X				
Inclusion/Exclusion	X				
Demographics	X				
Medical History	X				
Concomitant Medications	X	X	X	X	X
Gynecological Symptom Assessment	X	X	X	X	X
Gynecological Exam (visual inspection, infection assessment, vaginal discharge, and vaginal pH)	X	X	X	X	X
Packaging/Labeling Interview	X				
Randomization	X				
Test Article and Diary Dispensation	X	X*	X*		
Diary Training	X	X*	X*		
Test Article Collection (used and unused products)		X		X	
Diary Review		X		X	
Tampon Integrity Assessment		X		X	
Adverse Event Collection		X	X	X	X
Study Completion				X	

*As needed

Key:

X	Conducted for all subjects
X	Conducted for a subset of 120 subjects (Note, Visit 3 is only required for this subset of subjects)

3 TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition
AE	adverse event
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HPV	human papillomavirus
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Independent Review Board
KCC	Kimberly-Clark Corporation
PID	Pelvic Inflammatory Disease
SAE	serious adverse event
TSS	Toxic Shock Syndrome

INTRODUCTION

Feminine hygiene products are used by women throughout the world during their menstrual periods, from the onset of menarche until menopause. These products, which include pads, liners and tampons, function to contain and absorb menstrual fluid. Industrially manufactured tampons were first introduced into the US market in 1936. Since then, billions of tampons have been sold worldwide.

The primary indication for tampon use is for the absorption of menstrual fluid inside the vagina during the menstrual period. Modern tampons have been safely used as a convenient aid in managing menstrual discharges. About 90% of all girls in the United States are menstruating by 14 years of age, with a median age of approximately 12 years. This age at menarche is not significantly different than that reported for girls in the United States 47 years ago.[1] The average age for the end of menstruation, menopause, is approximately age 52 years among healthy women in United States.[2] However, there is growing evidence that menarche and menopause may be influenced by health status, ethnicity, genetic and socio-economic factors to some extent.[1,3]

Tampons are available in various absorbency ranges: light (<6 g), regular (6-9 g), super (9-12 g), super plus (12-15 g), and ultra (15-18 g). [redacted] are available in Regular, Super and Super Plus absorbencies. Currently marketed tampons consist of 100% cotton, 100% rayon, or blends of cotton and rayon absorbent materials. Tampons can be manufactured with or without an overwrap (cover). Additionally, they are available with different modes of insertion; either they are inserted with the finger (digital tampons) or with an applicator. Material and design changes of marketed tampons may have a potential effect on safety.

The tampons used in this study include a current commercially available [redacted] tampon and a modified [redacted] tampon. The radially wound design of the current [redacted] tampon can occasionally lead to an extending (i.e., telescoping or elongation) of the tampon upon removal due, in part, to the placement of the string. Kimberly-Clark (K-C) has modified the current [redacted] tampon to adjust the string placement in an effort to decrease this extension. This is a design validation study to validate the following user needs as they relate to the modified tampon: 1) product to remain clean prior to use, 2) product to remain in working condition prior to use, 3) user can access the product, 4) user can vaginally insert and place the tampon, 5) user can remove product from the vagina after use, 6) user can distinguish between absorbency levels, 7) product absorbs fluid, and 8) packaging is labeled properly.

5 TRIAL OBJECTIVES AND PURPOSE

Objective

The objective of this study is to validate that changes in the design of the [redacted] tampons meet defined user needs.

Primary Endpoint

The proportion of used tampons that have elongated will be used to assess the following user need:

- User can remove product from the vagina after use

Analysis will be done separately for each absorbency.

Key Secondary Endpoints

Diary responses will be used to assess the following user needs:

- Product to remain clean prior to use
- Product to remain in working condition prior to use
- User can access the product
- User can vaginally insert and place the tampon
- User can remove product from the vagina after use
- Product absorbs fluid

Analysis will be done separately for each absorbency.

Interview responses will be used to assess the following user need:

- User is able to distinguish between absorbency levels
- Packaging is labeled properly

Interview responses will only be done for both absorbencies combined.

Product tolerability will be evaluated through the following measures:

- Gynecological exam findings
- Frequency and severity of adverse events

6 INVESTIGATIONAL PLAN

Overall Study Design

This prospective multi-center, open-label, randomized, cross-over study is designed to validate that changes to the design of [redacted] tampons meet the following user needs: product to be safe, product to remain clean prior to use, product to remain in working condition prior to use, to be able to access the product, to be able to vaginally insert and place the tampon, to be able to remove product from the vagina after use, product to absorb fluid, to be able to distinguish between absorbency levels, packaging to be labeled properly.

Subjects will be assigned to one of two arms in the study: a regular absorbency arm or a super absorbency arm. Within each arm, a subset of 60 subjects will undergo gynecological exams prior to and following tampon use.

Subjects will be randomly assigned the order in which to test a new tampon design (test tampon) and a currently marketed tampon (reference tampon). Each tampon type will be used over the course of one (1) menstrual cycle. Subjects will be provided with 16 tampons per menstrual cycle.

For subjects undergoing gynecological exams, the study consists of 4 visits for each study subject, 2 visits for each menstrual cycle: one before and after each menstrual cycle. The first visit will be both the screening and the first pre-use visit. Pre-use visits will be conducted within 72 hours prior to expected menstruation. Post-use visits are to be completed within 72 hours following the last tampon use for that menstrual cycle. Subjects will undergo gynecological exams at each visit. Subjects will keep a daily diary during menstruation with entries for every tampon use. Subjects will also collect each used tampon to be returned to the clinical site for inspection by study staff to assess tampon integrity. Additionally, these subjects will complete an interview during the first visit to assess whether the subject can locate key information on the product packaging.

For the remainder of the subjects, the study will consist of 3 visits for: a screening and pre-use visit, and two post-use visits. Post-use visits are to be completed within 72 hours following the last tampon use for that menstrual cycle. Subjects will keep a daily diary during menstruation with entries for every

tampon use. Subjects will also collect each used tampon to be returned to the clinical site for inspection by study staff to assess tampon integrity.

Duration of subject participation in the study will be approximately 2 months.

Number of Subjects

The study population consists of 2 arms of approximately 369 females (total 738 subjects), ages 18-49, in good general health, in the United States who normally use tampons for menstrual protection, menstruate regularly, and do not have a history of Toxic Shock Syndrome (TSS).

Treatment Assignment

Subjects will be assigned to one of two arms in the study based on the absorbency of tampon the subject uses most often: a regular absorbency arm or a super absorbency arm. The order of using the test and reference tampons will also be randomly assigned.

Criteria for Study Terminations

The Sponsor may terminate this study, after informing Investigators, at any time for safety or administrative reasons. Investigators will be notified by the Sponsor or designee if the study is placed on hold, completed, or closed.

7 SUBJECT POPULATION

The study population consists of 2 arms of approximately 369 females (total 738 subjects), ages 18-49, in good general health, in the United States who normally use tampons for menstrual protection, menstruate regularly, and do not have a history of Toxic Shock Syndrome (TSS). One arm will test regular absorbency tampons and the other will test super absorbency tampons. Within each of these arms, a subset of 60 subjects will undergo gynecological exams before and after product use.

Subject Inclusion Criteria

Women who meet all the following inclusion criteria will be eligible for participation in the study:

1. Willing and able to read and provide written informed consent.
2. Female in good general health, age 18-49 (inclusive).
3. Last pap smear was normal in the past 3 years, or a normal pap with a negative HPV in the past 5 years, or negative HPV in the last five years (age <21 does NOT need a PAP or HPV result) based on self-report
4. History of regular menstrual cycles during the previous 3 months lasting approximately 21-35 days, including at least 4 days of menstruation, and expecting to menstruate during the study period.
5. Tracks menstruation and able to confidently predict onset of menstruation within 72 hours.
6. History of use of applicator tampons without discomfort.
7. Normally use at least 6 tampons for protection during menstruation.
8. Normally uses regular, super, and/or super plus absorbency tampons for menstrual protection.

9. If uses super plus absorbency, must be willing to wear nothing greater than super absorbency for the duration of the study.
10. Agrees not to use douching substances, vaginal medications, suppositories, or vaginal devices for the duration of the study.
11. **[For subjects undergoing gynecological exams only]** Agrees not to apply feminine deodorant spray, powders, perfumes, wipes, lotions, creams or emollients to the genital area for at least 24 hours prior to each visit.
12. Agrees not to try any new products in the vaginal/perineal area two (2) weeks prior to the study start and for the duration of the study.
13. Agrees to the conduct of all study procedures, including gynecological exams (if applicable), and agrees to follow all study instructions and return for scheduled appointments.
14. Has used an acceptable form of birth control for at least one month prior to enrollment and for the duration of the study. Acceptable methods include hormonal contraceptive, IUD, tubal ligation, partner vasectomy, condom (with or without spermicide), or abstinence.

Subject Exclusion Criteria

Women who meet any the following exclusion criteria will NOT be eligible for participation in the study:

1. Pregnant, lactating or is trying to become pregnant.
2. Less than six (6) weeks post-partum.
3. Has a menstrual abnormality (such as oligomenorrhea or amenorrhea).
4. History of any of the following diagnoses based on self-report: diabetes, active genital herpes lesion in last 3 years, Human Immunodeficiency Virus (HIV), Pelvic Inflammatory Disease (PID), Toxic Shock Syndrome (TSS).
5. History of an abnormal pap smear within the last 3 years, positive HPV in the last 5 years, any form of gynecological cancer, or gynecological disorder such as fibroids, or endometriosis (by self-report). Participants that have had a history of an abnormal pap smear, but most recent pap smear has been normal, may be included.
6. Has a medical condition which might compromise her immune system functions (such as cancer, immunosuppressive therapy, anemia currently being treated under the care of a physician, leucopenia, HIV-positive, or organ transplant).
7. Has used steroid medications (systemic or topical) for fourteen (14) or more consecutive days within the last sixty (60) days.
8. **[For subjects undergoing gynecological exams only]** Has Type B (petechia, ecchymoses) or C (peeling, abrasions, ulcerations, or lacerations) lesions on the perineum, vulva, urethra, vagina, or cervix as determined by the investigator at the screening visit.
9. **[For subjects undergoing gynecological exams only]** Has Type A (erythema or edema) lesions covering >50% of any of the perineum, vulva, urethra, vagina, or cervical locations as determined by the investigator at the screening visit.
10. Has had clinically identified genital warts/lesions and/or urogenital infection (such as bacterial vaginosis, Trichomoniasis, yeast infection, Chlamydia trachomatis, Neisseria gonorrhea, or a urinary tract infection) within the past 6 weeks.

11. Has a known allergy or sensitivity to components of the investigational products, including rayon.
12. Any other medical condition or history, as determined by the Investigator that could compromise the study results or subject safety.

Subject Withdrawal Criteria

Subjects may be withdrawn or terminated from the study for any reason and documented as one of the following:

1. Emergence of a severe condition such that, in the opinion of the Investigator, continuation in the trial would negatively impact the health of the subject.
2. Personal reasons (e.g., withdrawn consent)
3. Subject lost to follow-up
4. Sponsor decision
5. Clinical trial close-out

The reason for study discontinuation and date of study withdrawal will be documented.

The site staff must document their attempts to contact subjects who are lost to follow-up.

8 STUDY CONDUCT AND PROCEDURES

Subjects will be assigned to one of two arms in the study: a regular absorbency arm or a super absorbency arm. Subjects will be assigned to the regular or super absorbency arm based on the tampon absorbency they use most often. Within each arm, a subset of 60 subjects will undergo gynecological exams prior to and following tampon use.

Subjects will be randomly assigned the order in which to test a new tampon design (test tampon) and a currently marketed tampon (reference tampon). Each tampon type will be used over the course of one (1) menstrual cycle. Subjects will be provided with 16 tampons per menstrual cycle.

Intended Use of Test Article

The [redacted] Regular, Super, and Super Plus absorbency tampons are over the counter medical devices intended to be inserted into the vagina by menstruating females for the absorption of menstrual fluid, after which is removed and discarded. The population of individuals that will use these devices are menstruating females of any age. In the United States, tampons are Class II medical devices per 21 CFR 884.5470 (Unscented Menstrual Tampons).

Description of Test Article

The [redacted] tampon is a [redacted] tampon in an applicator. The applicator aids in insertion of the tampon device into the vagina during menstruation and is removed after deployment. The removal of the tampon involves an attached [redacted] string which extends externally for ease of access.

The [redacted] device consists of a tampon (absorbent core, overwrap cover and withdrawal string) in a three-piece applicator individually wrapped in a printed plastic film. The tampon is composed

of a [redacted] absorbent core, a [redacted] overwrap cover that surrounds the [redacted] core, and a white or pink rayon/polyester string [redacted] to enable tampon removal. [redacted]

The three-piece applicator consists of an outer insertion tube, referred to as the barrel, which has a textured grip and closed rounded tip in a petal-like design at the distal end (end of the applicator closest to the cervix during tampon insertion). The applicator also includes a short inner tube, referred to as a plunger, which snaps into place with a short middle telescopic tube to form an elongated plunger of the proper length to expel the tampon from the applicator barrel into the vagina. The applicator barrel holds the tampon prior to use, and the withdrawal string of the tampon is threaded through the telescope/plunger tube and a portion remains outside the applicator prior to use. [redacted]

The final tampon product was subjected to extensive biocompatibility testing per FDA guidance and current ISO 10993 biocompatibility testing guidance for class II medical devices with additional assessments for tampons. [redacted]

This study will include two absorbencies of [redacted] tampon: regular and super. [redacted] tampons have been marketed in the United States for more than 10 years. The composition of the modified tampon is the same as described above, but with an adjusted placement of the withdrawal string.

Concomitant Medications

Medication use within 30 days of Visit 1 and throughout the duration of the subject's participation will be recorded.

Randomization

Subjects will be assigned a unique subject identification number by the site at screening. Following completion of the screening procedures, eligible subjects will be assigned to either the regular or super absorbency arm, based on the tampon absorbency the subject uses most often. Within each arm, the order in which the test and reference tampons will be used will be randomized.

A randomization schedule that was created by the unblinded biostatistician at [redacted] will be provided to each site. Unique subject randomization numbers will be assigned by the site according to the site specific randomization schedule. Randomization numbers should be assigned sequentially within each arm.

Exam Procedures

A subset of 60 subjects in each arm will undergo a gynecological examination at each visit. Gynecological exams may also be conducted as needed for any subject to assess adverse events.

The following will be included in the exam:

- Symptom assessment

Prior to the vaginal exam, subjects will be asked to complete a short questionnaire regarding vaginal symptoms they may be experiencing. The purpose of this assessment is to alert the clinician of any possible conditions that may need to be addressed for the health of the subject and that may affect eligibility.

- Visual assessment
  This gynecological exam will consist of a visual inspection of the perineum, vulva, urethra, vagina, and cervix. Use of a clear speculum and light are expected for this exam. Each anatomical location will be evaluated for lesions. Each lesion will be characterized according to one of the following types[4]:

Type	Epithelium	Blood Vessel	Description	Coverage	Comment
A	Intact	Intact	☐ Erythema ☐ Edema	☐ ≤ 50% ☐ > 50%	*Provide specific location and any other relevant findings*
B	Intact	Disrupted	☐ Petechia ☐ Ecchymoses	☐ ≤ 50% ☐ > 50%	
C	☐ Disrupted, superficial ☐ Disrupted, deep	☐ Intact ☐ Disrupted	☐ Peeling ☐ Abrasion ☐ Ulceration ☐ Laceration	☐ ≤ 50% ☐ > 50%	
D	N/A	N/A	☐ Other	☐ ≤ 50% ☐ > 50%	*Provide description of the lesion, specific location, and any other relevant findings*

Type D lesions can be other lesions not related to epithelial or blood vessel disruption such as cysts, polyps, neoplasms, etc.

Subjects with presence of any Types B or C lesions at baseline will be excluded from the study. Subjects with a Type A lesion (erythema or edema) may be included as long as the coverage area is ≤ 50%. Subjects with Type D lesions will be excluded at the discretion of the investigator.

Superficial epithelial disruption does not penetrate into the subepithelial tissue. Deep epithelial disruption penetrates into and exposes the subepithelial tissue and possibly blood vessels. If bleeding from the finding is present, the disruption should be recorded as deep[5].

Lesions identified after the screening visit will be considered adverse events. Severity is determined by disruption of the epithelium and blood vessels. Lesions with an intact epithelium and intact blood vessels are considered mild (Types A). Any lesion that has a deep disruption in the epithelium is considered severe (Type C with deep epithelial disruption). All others are considered moderate (Type B and Type C with superficial epithelial disruption). Severity of "Other" (Type D) lesions will be determined by the Investigator.

- Vaginal discharge

The quantity, odor, color, and consistency of the vaginal discharge will be assessed during the vaginal exam by the investigator to determine whether a vaginal infection is suspected.

- Vaginal pH

  Vaginal pH measurements should be taken using pH testing strips and instructions provided. The testing strips measure pH in increments of 0.5, with a minimum range of 4.5 – 7.5.

- Suspected infection

  A subject who has symptoms of a vaginal infection or urinary tract infection at screening is not eligible to participate in the study. If a subject develops a vaginal infection or UTI during the study, she will stop using the study product and switch to menstrual pads. The subject may be treated by the investigator or referred for treatment at the discretion of the investigator. Subjects may continue using study product after treatment is complete and symptoms have resolved, if appropriate for the study design. Development of vaginal infections after screening are recorded and analyzed as adverse events.

- Other abnormal findings

  Any other abnormal findings during the vaginal examination will be recorded. Subjects may be excluded for abnormal findings. Abnormal findings recorded after the screening visit will be recorded and analyzed as adverse events.

Tampon Assessment Procedures

Each used tampon will be collected within a clear plastic sealable bag and frozen until returned to the study site. Tampons will be collected by study staff, removed from the bag, and photographed using standardized photography set-up. Study staff will measure elongation of each used tampon using a provided calibrated ruler. If elongation occurs, measurements will be taken to the nearest mm from the base of the tampon to the furthest point of the absorbent material protruding from the base. If no elongation occurs, a value of 0 mm will be recorded. Any measurement >10 mm will be considered elongation.

9 TEST ARTICLE AND MANAGEMENT

Test Article(s)

- Modified [redacted] Tampons (test tampons)
  - Regular Absorbency – Code Letter: BR
  - Super Absorbency – Code Letter: BS
- Commercial [redacted] Tampons (reference tampons)
  - Regular Absorbency – Code Letter: CR
  - Super Absorbency – Code Letter: CS

Test Article Packaging and Labeling

All test articles will be packaged in boxes resembling commercial [redacted] tampon packaging. Each box will contain 16 tampons and a commercial product insert containing general tampon usage instructions, as well as applicable safety information. Each box will minimally contain the following information:

- study number
- applicable test article code letters (BR, BS, CR, or CS)
- absorbency level
- quantity of the contents
- the name and place of business of the manufacturer
- the statement, "CAUTION - Investigational device. Limited by Federal (or United States) law to investigational use."

Test Article Accountability

With each shipment of test articles, investigative sites will receive a copy of the study material packing listing the details of the contents of the shipment. Investigative sites should sign and date the enclosed packing list and verify receipt of the shipment. The original signed packing list should be retained in the site's regulatory document repository. Packing lists will be reviewed, and any items received by the site, including their lot numbers and code letters, will be documented in the accountability log. Copies of the accountability log will be monitored for completeness and accuracy.

Test Article Dispensation, Collection, and Management

The following items will be dispensed to the subject at the visit prior to product use:

- 1 box of tampons according to the randomization schedule
- 1 used tampon collection kit containing the following:
  - 16 small clear sealable individual used tampon collection bags
  - 1 medium sized red sealable bag to collect all individually sealed tampon bags
- 1 diary containing study instructions and diary entry forms for each tampon used
- 1 cooler bag (dispense 1 per subject for the entire study)
- 1 freezer pack
- 1 large opaque white drawstring bag used to return the cooler bag containing the red tampon collection bag, completed diary, and any unused tampons to the site

Subjects will collect each used tampon and place it in a clear bag, labeled with the following information:

- Study Number
- Subject Number
- Menstrual Cycle (1 or 2)
- Tampon Number (e.g., #1, #2, #3, etc.)
- Tampon Code (CR, CS, BR, or BS)

Each of the clear bags containing a used tampon will be placed inside of the single red sealable bag and placed in the freezer until returned to the clinic. The red bag will be labeled with the following information:

- Study Number
- Subject Number
- Menstrual Cycle (1 or 2)

- Tampon Code (CR, CS, BR, or BS)

If a subject is not at home at the time of tampon removal, the subject can place the tampon in the clear collection bag in the cooler bag provided until the subject returns home and can place it in the red bag in the freezer.

Following the last tampon use, subjects will return to the clinic, with the following items in the white drawstring bag provided:

- cooler bag containing the red tampon collection bag with all used tampons
- completed diary
- all unused tampons.

Study staff will document the number of used and unused tampons collected, verify that there is a diary entry for each used tampon, verify the accuracy and completeness of diary entries, and address and document any discrepancies.

10 STUDY VISIT SCHEDULE

Subjects will be assigned to one of two arms in the study: a regular absorbency arm or a super absorbency arm. Within each arm, a subset of 60 subjects (Subset Population) will undergo gynecological exams prior to and following tampon use. The study visit schedule is the same for both arms of the study.

For subjects in the Subset Population, the study will consist of 4 visits for each study subject, 2 visits for each menstrual cycle: one before and after each menstrual cycle.

For all other subjects, the study will consist of 3 visits: a screening and pre-use visit, and two post-use visits.

Pre-use visits will be conducted within 72 hours prior to expected menstruation. Post-use visits are to be completed within 72 hours following the last tampon use for that menstrual cycle.

The schedule of visits and timing of procedures are summarized in the Proposed Schedule of Events (Table 1 - Proposed Schedule of Events).

Visit 1 – Screening/Baseline/Pre-Use Visit

For all subjects, Visit 1 will include the following:

- Signing of informed consent
- Review of inclusion and exclusion criteria
- Collection of demographic information
- Review of medical history
- Review of concomitant medications
- Questionnaire to determine type of tampon used historically
- Randomization
- Test article dispensation
- Diary training

For all subjects in Subset Population, Visit 1 will also include the following:

- Gynecological symptom assessment
- Gynecological exam (visual inspection, infection assessment, vaginal discharge, and vaginal pH)
- Packaging/labeling interview

Visit 2 – Post-Use Visit

For all subjects, Visit 2 will include the following:

- Test article collection (used and unused products)
- Diary review
- Test Article dispensation (if not in the Subset Population)
- Diary dispensation (if not in the Subset Population)
- Diary re-training, if needed
- Tampon integrity assessment
- Adverse event collection

For all subjects in Subset Population, Visit 2 will also include the following:

- Gynecological symptom assessment
- Gynecological exam (visual inspection, infection assessment, vaginal discharge, and vaginal pH)

Visit 3 – Pre-Use Visit

Visit 3 is only required for the Subset Population. It will include the following:

- Gynecological symptom assessment
- Gynecological exam (visual inspection, infection assessment, vaginal discharge, and vaginal pH)
- Test Article dispensation
- Diary dispensation
- Diary re-training, if needed

Visit 4 – Post-Use Visit

For all subjects, Visit 4 will include the following:

- Test article collection (used and unused products)
- Diary review
- Tampon integrity assessment
- Adverse event collection

For all subjects in Subset Population, Visit 4 will also include the following:

- Gynecological symptom assessment
- Gynecological exam (visual inspection, infection assessment, vaginal discharge, and vaginal pH)

11 STATISTICAL METHODS

Sample Size

The sample size was calculated for a single absorbency and is based on the assumption that 0.7% of reference tampons elongate (>10 mm) upon removal and 0.2% of test tampons elongate upon removal. An estimated yield of 43.75% was used, where yield is the number of usable tampons for the elongation analysis divided by the total number of products given to the subjects (i.e., yield means the percentage of tampons given to each subject that were used and can be included in the elongation analysis). It is assumed that subjects are given 16 reference tampons and 16 test tampons and use 7 tampons in each cycle.

With a power of 80% and 2-sided alpha of 0.05, assuming 2 tampon types tested (reference and test) and each subject receiving 16 products per cycle, a total of 369 subjects will need to be enrolled in the study for each absorbency. Since there are 2 absorbencies the study will enroll 738 subjects.

For each absorbency this translates into needing a total of 5,166 used tampons (2,583 used tampons for each tampon type (reference and test)).

Analysis Populations

Intent-to-Treat (ITT): Subjects randomized into the study.

Safety: ITT subjects who insert at least 1 tampon

Modified Intent-to-Treat (MITT): Safety subject who returns at least 1 tampon that can be assessed for elongation.

Primary Endpoint

The proportion of used tampons that have elongated will be used to assess the following user need:

- User can remove product from the vagina after use

Analysis will be done separately for each absorbency for the MITT population.

Key Secondary Endpoints

Diary responses will be used to assess the following user needs:

- Product to remain clean prior to use
- Product to remain in working condition prior to use
- User can access the product
- User can vaginally insert and place the tampon
- User can remove product from the vagina after use
- Product absorbs fluid

Analysis will be done separately for each absorbency using the Safety population.

Interview responses will be used to assess the following user needs:

- User is able to distinguish between absorbency levels
- Packaging is labeled properly

Interview responses will only be done for both absorbencies combined for the ITT population.

Product tolerability will be evaluated through the following measures:

- Gynecological exam findings
- Frequency and severity of adverse events

Analysis will be done separately for each absorbency using the Safety population.

Validation Criteria

The primary objective of this study is to validate that changes in the design of the [redacted] tampons meet defined user needs. The primary objective will have been met if the following criteria are met:

- Test tampon elongation rate is the same as or better than the reference tampon for each absorbency, where same is defined as test tampon elongation rate ≤ reference tampon elongation rate .
- Product tolerability is deemed to be acceptable based on review of the results.
- Diary responses have ≥ 96% response rates consistent with each user need for each absorbency. If the rate is lower than 96%, the response rate consistent with the user need related to the test tampon must be the same as or better than the response rate of the reference tampon, where same is defined as test tampon response rate ≥ reference tampon response rate.
- Interview responses demonstrate that 95% of users are able to identify key information on the package and insert, and able to distinguish between absorbency levels on the wrappers.

12 ASSESSMENT OF SAFETY

Anticipated Risks

The risks associated with study participation are similar to those previously identified with all tampons, including adverse tissue reactions, vaginal injury, vaginal infection, pain, discomfort, allergy, and Toxic Shock Syndrome (TSS).

Definition of Adverse Event

An AE is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in a clinical investigation subject, whether or not related to the investigational medical device.

Definition of Serious Adverse Event

Seriousness is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. An SAE is defined as any untoward medical occurrence that falls into one of the following categories:

- Results in death
- It is immediately life-threatening

- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Intervention required to prevent permanent impairment
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

All SAEs that occur after any subject has been enrolled, before treatment, during treatment, or within 7 days following the cessation of treatment, whether or not they are related to the study, must be recorded on forms provided by Kimberly-Clark.

Definition of an Unanticipated Adverse Device Effect (UADE)

An UADE is defined as any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects**.**

Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Information about AEs will be collected from the Test Article Dispensation until the end of the study. Serious Adverse Event information will be collected from Test Article Dispensation until 7 days following Visit 4 (Post-use Visit). The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, frequency, relationship to test article, action taken, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. An AE of severe intensity may not be considered serious.

Relationship to test article will be assessed according to the following scale:

- Not Related - A clearly evident relationship to other etiologies exists and/or the event is not temporally consistent with test article use.
- Unlikely - Based upon available information, a causal relationship to test article is improbable. Usually, another cause is most plausible.
- Possible - Event follows a reasonable temporal association with test article use and is clinically/biological plausible. Other etiologies are also possible.
- Probable - A reasonable temporal sequence of the event with test article use exists and based upon the medical professional's clinical experience, the association of the event with test article seems very likely.

- Definite - Event is clearly related to article use. It is temporally associated with test article use, follows a known or expected response pattern, and improves when stopping test. Other causes do not appear to explain the event.

Reporting Adverse Events

All SAEs (related and unrelated) will be recorded from the Test Article Dispensation until 7 days following Visit 4 (Post-use Visit). Any SAEs considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to Kimberly-Clark within one business day of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by email to the Medical Monitor at [redacted] Additional follow-up information, if required or available, should all be emailed to the Medical Monitor within one business day of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the CRF and/or study file.

Kimberly-Clark is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, adverse device effects that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

Collection and Reporting of Commercial Product Complaints

A Product Complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is commercially available. Upon the return of the Study Diary, each entry will be reviewed for completeness and possible AEs. Any potential AEs will be assessed, documented, and reported according to the defined serious and non-serious adverse event reporting parameters outlined above.

Any SAE possibly, probably, or definitely related to a commercially available test product (codes CR and CS) will be evaluated for reportability to applicable regulatory agencies by Kimberly-Clark according to the Safety Monitoring Plan.

The Medical Monitor will be notified of all non-serious AEs that are possibly, probably, or definitely related to a test product upon entry of the data into the electronic data capture (EDC) system. Those AEs that are related to a commercially available test product (codes CR and CS) will be evaluated for reportability to applicable regulatory agencies by Kimberly-Clark according to the Safety Monitoring Plan.

The Medical Monitor will be notified of potentially reportable complaints related to commercially available test products that are not associated with an AE upon entry of the diary data into the EDC system. Kimberly-Clark will evaluate for reportability to applicable regulatory agencies as documented in the study Safety Monitoring Plan.

All other non-reportable complaints will be reviewed by Kimberly-Clark in aggregate following completion of the study report.

13 ETHICS

Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to Kimberly-Clark or designee before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Ethical Conduct

The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 812, and the ICH E6.

Written Informed Consent

Informed consent will be obtained in accordance with International Council for Harmonisation-Good Clinical Practice, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA), if applicable, and local regulations.

The Principal Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

14 REFERENCES

1. Chumlea WC, Schubert CM, Roche AF, Kulin HE, Lee PA, Himes JH, Sun SS. Age at menarche and racial comparisons in US girls., Pediatrics. 2003 Jan;111(1):110-3. https://doi.org/10.1542/peds.111.1.110 (last accessed 18 Jan 2022)
2. Shifren, J.L., Gass, M.L.S., for the NAMS Recommendations for Clinical Care of Midlife Women Working Group. (2014). The North American Menopause Society Recommendations for Clinical Care of Midlife Women. Menopause; 21(10): 1038–1062. doi: 10.1097/GME.0000000000000319
3. Luoto R1, Kaprio J, Uutela A., Age at natural menopause and sociodemographic status in Finland. Am J Epidemiol. 1994 Jan 1;139(1):64-76 doi: 10.1093/oxfordjournals.aje.a116936.
4. Harwood, B, et al. Cervicovaginal colposcopic lesions associated with five Nonoxynol-9 vaginal spermicide formulations. *Am J Obstet Gynecol.* 2008;198(1): 32.e1–32.e7. doi:10.1016/j.ajog.2007.05.020
5. CONRAD/WHO. Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2000. Geneva: CONRAD/WHO; 2000. CONRAD/2000.1, WHO/RHR/00.11