Clinical Study Plan

Study ID SU020

A Post-Market Evaluation of the Altis® Single Incision Sling System versus Transobturator or Retropubic Mesh Sling in the Treatment of Female Stress Urinary Incontinence (Altis 522 Study)

Sponsor
Coloplast Corp
1601 W. River Rd.
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Version 4.0

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Synopsis of the Clinical Study

The aim of this postmarket study is to compare the safety and effectiveness of the Altis Single Incision Sling (SIS) to an FDA cleared transobturator and/or retropubic mesh sling through 36 months. The primary safety and effectiveness objectives are as follows:

Primary Safety Objective

To demonstrate that the rate of device and/or procedure related serious adverse events associated with use of Altis SIS is non-inferior compared to the rate associated with use of transobturator and/or retropubic slings at 36 months.

Primary Effectiveness Objective

To demonstrate that the rate of effectiveness associated with use of Altis SIS is non-inferior to the rate associated with use of transobturator or retropubic mesh slings for the treatment of stress urinary incontinence at 6 months.

This study is a prospective, post-market, multi-center, cohort assessment comparing Altis SIS (n=178) and transobturator and/or retropubic slings (n=178) in the treatment of stress urinary incontinence, at up to 40 U.S. and International sites. Subjects will be followed for a total of 36 months with scheduled visits at 6 months, 12 months, 18 months, 24 months, and 36 months.

The study population will consist of adult female subjects with stress urinary incontinence who are clinically indicated for surgical intervention with a mesh sling. All study candidates who provide written informed consent and meet all of the inclusion criteria and none of the exclusion criteria will be included in the study.

Endpoints

Primary Safety Endpoint

- Observed device and/or procedure-related serious adverse events through 36-months.

Primary Effectiveness Endpoint

- Observed effectiveness, defined as a reduction from baseline in 24 hour pad weight of at least 50% at 6 months.

Secondary Safety Endpoints

- Observed rates of device and/or procedure-related adverse events defined as organ perforation, bleeding, mesh exposure in the vagina, mesh erosion into the bladder, pelvic pain, infection, de novo dyspareunia, urinary retention, recurrent incontinence, other urinary problems and neuromuscular problems at 6 months, 12 months, 18 months, 24 months, and 36 months post index procedure.

- All observed adverse events at 6 months, 12 months, 18 months, 24 months, and 36 months.

- Observed revision/re-surgery at 6 months, 12 months, 18 months, 24 months, and 36 months.

Secondary Effectiveness Endpoints

- Observed effectiveness defined as a reduction from baseline in 24 hour pad weight of at least 50% at 12 months, 18 months, 24 months, and 36 months.

- Observed effectiveness for subjects considered dry (pad weight ≤ 4.0 grams) at 6, 12, 18, 24, and 36 months.

- Quality of Life at 6 months, 12 months, 18 months, 24 months, and 36 months as measured through:
    - Patient Global Impression of Improvement (PGI-I)
    - Urogenital Distress Inventory (UDI-6)
    - Incontinence Impact Questionnaire-Short Form (IIQ-7)
    - Surgical Satisfaction Questionnaire (SSQ-8)
    - Visual Analog Scale for Pain (VAS Pain)

Inclusion Criteria for Subject Selection

To be included in the study, subjects must meet all of the following inclusion criteria:

1. The subject is female and at least 18 years of age.
2. The subject is able and willing to complete all procedures and follow-up visits indicated in this protocol.
3. The subject has confirmed stress urinary incontinence (SUI) through cough stress test or urodynamics.
4. The subject has failed two non-invasive incontinence therapies (such as Kegel exercise, behavior modification, pad use, biofeedback, etc.) for > 6 months.

Exclusion Criteria for Subject Selection

To be included in this clinical study subjects must not meet any of the following exclusion criteria:

1. The subject has an active urogenital infection or active skin infection in region of surgery.
2. The subject has confirmed Pelvic Organ Prolapse (POP) of Stage 2 or higher as determined by POP-Q prolapse grading.
3. The subject is having a concomitant pelvic floor procedure.
4. The subject has incontinence due to neurogenic causes (e.g. multiple sclerosis, spinal cord/brain injury, cerebrovascular accident, detrusor–external sphincter dyssynergia, Parkinson’s disease, or similar conditions).
5. The subject had a prior surgical SUI treatment.
6. The subject has undergone radiation or brachy therapy to treat pelvic cancer.
7. The subject has urge predominant incontinence by MESA assessment.
8. The subject has an atonic bladder or post void residual (PVR) above 100 cc on ≥ 2 occasions.

9. The subject is pregnant and/or is planning to get pregnant in the future.
10. The subject has a contraindication to the surgical procedure or the product IFU.
11. The subject is enrolled in a concurrent clinical trial of any treatment (drug or device) that could affect continence function, without the sponsors' approval.

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
CEC	Clinical Events Committe
CRF/eCRF	Case Report Form/Electronic Case Report Form
CTM	Clinical Trial Manager
EC	Ethics Committee
EDC	Electronic Data Capture
FDA	Food and Drug Administration
IFU	Instructions for Use
IIQ-7	Incontinence Impact Questionnaire (IIQ-7)
IRB	Institutional Review Board
ISO	International Organization for Standardization
MESA	Medical, Epidemiologic, and Social Aspects of Aging
MUI	Mixed Urinary Incontinence
OAB	Over Active Bladder
PGI-I	Patient Global Impression of Improvement (PGI-I) – Incontinence
PI	Principal Investigator
PP	Per Protocol
QoL	Quality of Life
SAE	Serious Adverse Event
SIS	Single Incision Sling
SSQ	Surgical Satisfaction Questionnaire
SUI	Stress Urinary Incontinence
TO	Transobturator
TOT	Transobturator Technique
TVT-O	Tension-free Vaginal Tape--Obturator
UADE	Unanticipated Adverse Device Effect
UDI-6	Urinary Distress Index (UDI-6)
UTI	Urinary Tract Infection

ABBREVIATION	DEFINITION
UUI	Urge Urinary Incontinence
VAS	Visual Analog Scale

SIGNATURE PAGE

All parties hereby declare to follow the Clinical Study Plan in accordance with the Declaration of Helsinki, ICH E6 Good Clinical Practice, ISO 14155, the Medical Device Directive and appropriate FDA regulations, as applicable.

SPONSOR

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APPROVER

Dale Klous
Director of Clinical Science and Office of Medical Affairs

12 Nov 2018
Date

CLINICAL TRIAL MANAGER

Kris Veltum
Senior Clinical Trial Manager

09-Nov-2018
Date

STATISTICIAN

Kaisa Kivilaid,M.S.
Biostatistician

09-Nov-2018
Date

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

All parties hereby declare to follow the Clinical Study Plan in accordance with the Declaration of Helsinki, ICH E6 Good Clinical Practice, ISO 14155, the Medical Device Directive and appropriate FDA regulations, as applicable.

NAME AND TITLE:

ADDRESS:

POSTAL CODE AND CITY:

COUNTRY:

PHONE NUMBER:

[Principal Investigator Signature] [Date]

1 List of personnel involved in the study

1.1 Sponsor representatives

CLINICAL TRIAL MANAGER	STATISTICIAN
Kris Veltum Coloplast 1601 West River Rd N Minneapolis, MN Phone: (763) 248-5744 Email: uskve@coloplast.com	Kaisa Kivilaid, M.S. RCRI 5353 Wayzata Blvd, Suite 505 Minneapolis, MN Phone: (952) 746-8080 Email: kkivilaid@rcri-inc.com
COUNTRY SPECIFIC REPRESENTATIVE(S)	**MEDICAL ADVISOR**
NA	NA

1.2 Investigators

A list of all investigators participating in the study will be maintained in the trial master file at Coloplast.

1.3 Other Representatives

Study management activities including but not limited to database development may be outsourced to appropriate vendors.

2 Study Justification

Urinary incontinence (UI) is defined as the complaint of any involuntary loss of urine.[1] It is a common and distressing medical disorder which is associated with significant decrements in function and quality of life. (QoL). Age, BMI, race, medical comorbidity, current major depression, a history of hysterectomy, parity, and having only had cesarean deliveries are each independent factors significantly associated with the likelihood of having UI.[2]

Types of urinary incontinence include stress, urge, and mixed incontinence.[1,3] Stress Incontinence (SUI) is the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing. Urge Incontinence is the complaint of involuntary leakage accompanied by or immediately preceded by urgency. Mixed Incontinence is the complaint of involuntary leakage associated with urgency and also with effort, exertion, sneezing and coughing.[1]

Urinary incontinence affects up to 50% of all women and among these 50% to 80% are identified as having SUI. An estimated 4% to 10% of women in the United States undergo surgery intended to restore continence, and this rate has increased steadily during the past 20 years[4]. Additionally, it is commonly assumed by healthcare professionals that UI is an underreported condition, so the actual incidence rate may be much higher.[5]

Surgical treatment of SUI is the most common and the most effective. Surgical procedures performed for SUI increased from 18,820 to 32,480 from 1992 to 2001.[6] By 2001, more than half of the surgical procedures (17,680) were being done with a pubovaginal sling. The most common pubovaginal sling operations performed in the United States are the Tension-Free Vaginal Tape procedure (TVT)[7,8] and the transobturator technique (TOT).[8] In most respects, the TVT and TOT procedures are similar. Both place a hammock like mesh that passes underneath the urethra to provide support and exit through incisions in the abdomen. Tensioning is achieved by pulling the tape through the incisions and suturing the exit wounds. Minimally invasive or single incision slings or “mini-slings” are a recent development to address complications with the traditional slings. Mini-slings are placed through a single incision in the vaginal wall and anchored inside the body. This anchoring inside the body eliminates the exit wounds required for traditional slings. Mini-slings potentially reduce the risk of blind needle passage through the groin or abdomen and may be implanted in an office setting with local anethesia. All of these factors potentially reduce complications, recovery time, and pain compared to traditional slings.

The Altis Single Incision Sling (SIS) System was developed by Coloplast as a minimally invasive “mini-sling.” The Altis SIS System comprises a length of the same material used for the Aris™ Trans-Obturator and Supris™ Retropubic Slings. However, Altis is secured in the obturator foramen and has an integrated tensioning system that eliminates the need for additional skin exits. Effectiveness and safety outcomes of the Altis SIS Sling System were demonstrated in an Investigational Device Study conducted at 17 clinical sites in the United States and Canada. The Altis Sling System received FDA clearance on November 5, 2012, based on Coloplast's submission of IDE study data on 113 study subjects implanted with the Altis SIS.

Manufacturers of single-incision slings have been ordered to conduct post-market studies. These orders were issued on March 13, 2013 for the Altis SIS Sling System under Section 522 of the Federal Food, Drug, and Cosmetic Act. The reason for these orders is “that device failure would be reasonably likely to cause mesh erosion (i.e. organ perforation), severe pain, and fistula formation, which would meet the definition of "serious adverse health consequences" at 21 C.F.R. § 822.3(j)” and because the device is intended to be implanted in the body for more than one year.

3 Study Purpose and Design

3.1 Primary Objectives

The aim of this postmarket study is to compare the safety and effectiveness of Altis SIS to FDA cleared transobturator and/or retropubic slings in the treatment of stress urinary incontinence through 36 months. The primary safety and effectiveness objectives of this study are:

- To demonstrate that the rate of device and/or procedure related serious adverse events associated with use of Altis SIS is non-inferior compared to the rate associated with use of transobturator and/or retropubic slings at 36 months.

- To demonstrate that the rate of effectiveness associated with use of Altis SIS is non-inferior to the rate associated with use of transobturator or retropubic mesh slings for the treatment of stress urinary incontinence at 6 months.

3.2 Secondary Objectives

The secondary objectives of this study are:

- To demonstrate that the rate of device and/or procedure related adverse events defined as organ perforation, bleeding, mesh exposure in the vagina, mesh erosion into the bladder, pelvic pain, infection, de novo dyspareunia, urinary retention, recurrent incontinence, other urinary problems and neuromuscular problems associated with use of Altis SIS is non-inferior compared to the rate associated with use of transobturator and/or retropubic slings at 36 months.

- To demonstrate that the rate of revision/resurgery associated with use of Altis SIS is non-inferior compared to the rate associated with use of transobturator and/or retropubic slings at 36 months

- To provide a descriptive comparison at all time points (6 months, 12 months, 18 months, 24 months, and 36 months) between study groups of the rates associated with the following adverse events: organ perforation, bleeding, mesh exposure in the vagina, mesh erosion into the bladder, pelvic pain, infection, de novo dyspareunia, urinary retention, recurrent incontinence, other urinary problems and neuromuscular problems.

- To assess the effectiveness observed in both study groups at 6 months, 12 months, 18 months, 24 months, and 36 months.

- To assess Quality of Life in both study groups at 6 months, 12 months, 18 months, 24 months, and 36 months.

- To assess the rates, severity, and relatedness of all observed adverse events (including mesh exposure and erosion) associated with both study groups at 6 months, 12 months, 18 months, 24 months, and 36 months.

3.2.1 General

This study is a prospective, post-market, multi-center, cohort assessment comparing Altis SIS (Study Subjects) and transobturator and/or retropubic slings (Control Subjects) in the treatment of stress urinary incontinence. Subjects will be followed for 36 months, with scheduled follow-up visits at 6 months, 12 months, 18 months, 24 months, and 36 months.

The study will be analyzed under the intent-to-treat principle. A propensity score analysis will be used to address potential sources of bias due to the cohort design. Additional mechanisms to control potential sources of bias include: rigorous well-defined inclusion/exclusion criteria, utilization of screening and enrollment log, and consecutive enrollment of eligible subjects.

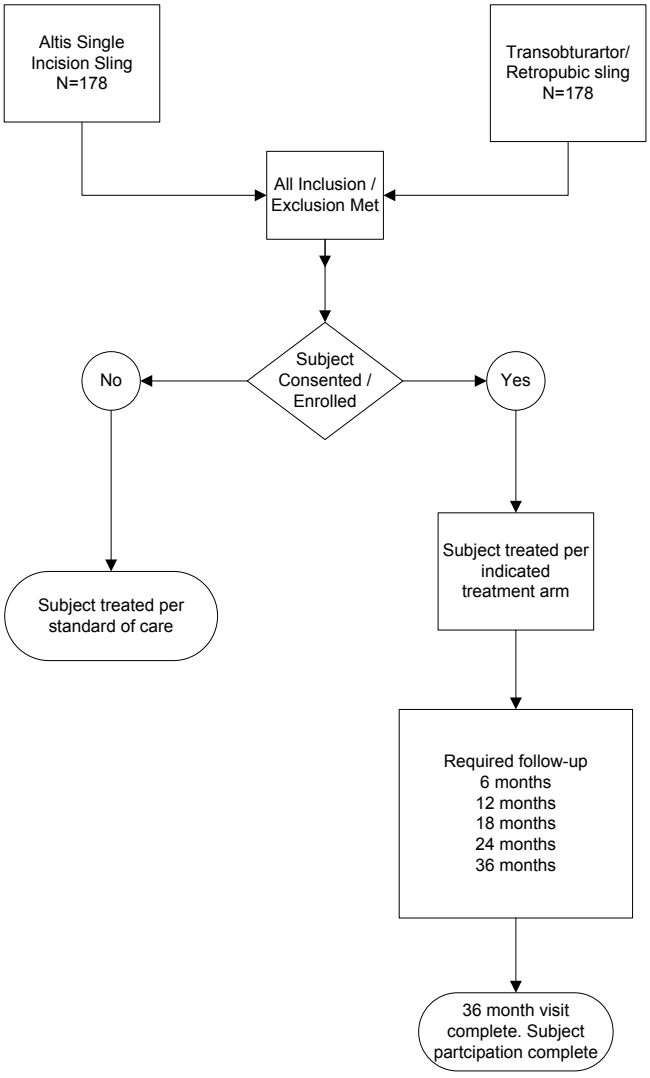
Treatment Group Subjects Altis Single Incision Sling	Control Group Subjects Transobturator or Retropubic Slings
N= 178	N= 178

Patient enrollment will continue until the required sample size is successfully reached. The study may include up to 40 U.S. and international sites. No site may attempt to implant more than 20% of subjects in each respective arm without prior approval from Coloplast Corp.

3.2.2 Site and Investigator Selection

Investigators experienced in the use of the study products for treatment of stress urinary incontinence will be recruited to participate in the study.

Figure 1: Overall Study Design Flow-Chart



3.3 Endpoints

3.3.1 Primary Safety Endpoints

- Observed device and/or procedure-related serious adverse events through 36-months.

3.3.2 Primary Effectiveness Endpoint

- Observed effectiveness, defined as a reduction from baseline in 24 hour pad weight of at least 50% at 6 months.

3.3.3 Secondary Safety Endpoints

- Observed rates of device and/or procedure-related adverse events defined as organ perforation, bleeding, mesh exposure in the vagina, mesh erosion into the bladder, pelvic pain, infection, de novo dyspareunia, urinary retention, recurrent incontinence, other urinary problems and neuromuscular problems at 6 months, 12 months, 18 months, 24 months, and 36 months post index procedure.

- Observed adverse events within 6 months, 12 months, 18 months, 24 months, and 36 months of the index procedure.

- Observed revision/re-surgery at 6 months, 12 months, 18 months, 24 months, and 36 months.

3.3.4 Secondary Effectiveness Endpoint

- Observed effectiveness, defined as a reduction from baseline in 24 hour pad weight of at least 50% at 12 months, 18 months, 24 months, and 36 months.

- Observed effectiveness for subjects considered dry (pad weight ≤ 4.0 grams) at 6, 12, 18, 24, and 36 months.

- Quality of Life at 6 months, 12 months, 18 months, 24 months, and 36 months as measured through:
    - Patient Global Impression of Improvement (PGI-I)
    - Urogenital Distress Inventory (UDI-6)
    - Incontinence Impact Questionnaire-Short Form (IIQ-7)
    - Surgical Satisfaction Questionnaire (SSQ-8)
    - Visual Analog Scale for Pain (VAS Pain)

3.3.5 Risk Factors

In addition to the primary and secondary endpoint analysis, a propensity analysis will be conducted to address potential risk factors of adverse events and procedural success. Risk factors that will be analyzed include but are not limited to:

- Age
- Parity
- BMI
- Smoking Status
- Diabetes
- Hysterectomy status
- History of Multiple Urinary Tract Infections

3.4 Subjects

The study population will consist of adult female subjects with SUI who are clinically indicated for surgical intervention with a mesh sling. All study candidates who meet all of the inclusion criteria and none of the exclusion criteria and provide written informed consent will be included in the study.

3.4.1 Inclusion criteria for subject selection

To be included in the study, subjects must meet all of the following inclusion criteria:

1. The subject is female and at least 18 years of age.
2. The subject is able and willing to complete all procedures and follow-up visits indicated in this protocol.
3. The subject has confirmed stress urinary incontinence (SUI) through cough stress test or urodynamics.
4. The subject has failed two non-invasive incontinence therapies (such as Kegel exercise, behavior modification, pad use, biofeedback, etc.) for > 6 months.

3.4.2 Exclusion criteria for subject selection

To be included in this clinical study subjects must not meet any of the following exclusion criteria:

1. The subject has an active urogenital infection or active skin infection in region of surgery.
2. The subject has confirmed Pelvic Organ Prolapse (POP) of Stage 2 or higher as determined by POP-Q prolapse grading.
3. The subject is having a concomitant pelvic floor procedure.
4. The subject has incontinence due to neurogenic causes (e.g. multiple sclerosis, spinal cord/brain injury, cerebrovascular accident, detrusor–external sphincter dyssynergia, Parkinson's disease, or similar conditions).
5. The subject had a prior surgical SUI treatment.
6. The subject has undergone radiation or brachy therapy to treat pelvic cancer.
7. The subject has urge predominant incontinence with MESA assessment.

8. The subject has an atonic bladder or post void residual (PVR) above 100 cc on ≥ 2 occasions.
9. The subject is pregnant and/or is planning to get pregnant in the future.
10. The subject has a contraindication to the surgical procedure or the product IFU.
11. The subject is enrolled in a concurrent clinical trial of any treatment (drug or device) that could affect continence function, without the sponsors' approval.

3.5 Subject Recruitment and Enrollment

Study subjects may be referred for surgical treatment of SUI by their primary care physician or specialist. Subjects must provide written informed consent prior to study-related procedures taking place. A screening and enrollment log will be maintained by study sites to document potential subjects who did not meet inclusion/exclusion criteria or who declined participation.

3.6 Point of Enrollment

Once the subject signs the approved informed consent form the subject is considered enrolled and a subject number is assigned.

3.7 Subject Withdrawal Criteria

The investigator may withdraw a subject from the study at any time if they judge withdrawal to be in the best interest of the subject for reasons including but not limited to the subject's safety and/or well-being.

Subjects are allowed to withdraw from the study at any time for whatever reason without any consequences to their future treatment outside the clinical study. If a participant expresses the desire to withdraw from the study, an end of study form must be completed. The reason for participant withdrawal must be documented.

In the case that the participant cannot be reached to return for protocol required follow-up visits, the study site must make at least 3 attempts to contact the subject (e.g. telephone, email). To be considered lost to follow-up, all attempts to contact the subject must be documented and a registered letter must be sent to the subject's last known address. In the case that the participant is determined to be lost to follow-up, an end of study form must also be completed.

If a subject withdraws, is lost to follow-up, or dies they will not be replaced by enrolling additional subjects. Participants will be considered to have completed the study after the 36-month follow-up visit has been completed.

3.8 Subject Retention

Subject follow-up visit compliance and long term retention of study subjects through 36-months is important. Every attempt should be made to complete the visit. If the follow-up visit cannot be completed within the established visit window, the visit should still be completed as soon as possible and a study deviation documented.

Additional strategies to maximize subject retention may include:

- Use of an IRB approved tiered subject visit compensation rate that increases over the course of the study
- Utilization of a follow-up window calculator tool to assist in targeting and scheduling future study follow-up visits
- Utilization of study specific appointment reminder cards and direct telephone contact

4 Total Expected Duration of the Clinical Study

Enrollment is expected to take approximately 2 years to complete and subjects will be followed for 36 months. The study will take approximately 5 years from first subject enrollment to final patient visit.

5 Procedures and Data Collection

Prior to site activation, all study personnel must receive formal study training from qualified personnel from Coloplast or its designee. This training will include, but is not limited to device design, clinical study protocol, case report form completion, regulatory requirements and required study procedures. Before initiation of the clinical study, the investigator must obtain Institutional Review (IRB) approval and the sponsor must be provided with a signed investigator agreement and dated curriculum vitae for key personnel to verify and document qualifications. The investigator must ensure that all site personnel are trained for delegated activities, e.g. study procedures, eCRF completion, and adverse event reporting.

Clinical data will be collected at baseline, procedure, 6 months, 12 months, 18 months, 24 months, and 36 months post index procedure. The Data Collection Schedule in Table 1 provides an outline of study data to be collected at each visit.

Additional visits that occur for adverse event assessment or adverse event follow-up following the index procedure will be recorded on an Unscheduled Visit and Adverse Event eCRF.

Table 1 Data Collection Schedule

Data Collection	Baseline	Procedure	6 Month	12 Month	18 Month	24 Month	36 Month	Un-scheduled[4]
Informed Consent Obtained	X							
Inclusion/Exclusion Criteria Verified	X							
Pregnancy Test	X[1]							
Urinalysis	X[2]							
Medical History	X							
Procedural Data		X						
Cystoscopy		X						
Post Void Residual Test	X[3]		X	X	X	X	X	
Cough Stress Test	X[3]		X	X	X	X	X	
24-Hour Pad Weight Test	X[3]		X[5]	X[5]	X[5]	X[5]	X[5]	
Medication Documentation	X	X	X	X	X	X	X	

Data Collection	Baseline	Procedure	6 Month	12 Month	18 Month	24 Month	36 Month	Un-scheduled[4]
Patient Global Impression of Improvement (PGI-I)			X	X	X	X	X	
Surgical Satisfaction Questionnaire (SSQ-8)			X					
Visual Analog Scale for Pain (VAS Pain)	X	X[6]	X					
Urinary Distress Index (UDI-6)	X		X	X	X	X	X	
Incontinence Impact Questionnaire (IIQ-7)	X		X	X	X	X	X	
Assessment of Adverse Events		X	X	X	X	X	X	X

[1]To be performed within 30 days prior to the index procedure for women of childbearing potential

[2] To be performed within 30 days prior to the index procedure

[3] To be performed within 6 weeks prior to index procedure

4 Any procedures performed relevant to the continence state of the subject should be documented on the follow-up form (e.g. PVR, urinalysis, or CST testing).

5 It is recommended that subjects complete pad weight testing within ± 1 month of the scheduled visit.

6 The VAS Pain questionnaire will be completed by subjects at baseline, each day for the first 3 days following their index procedure, and at their 6 month follow-up visit.

5.1 Baseline Visit

The following study procedures will be performed at or prior to (as described in Table 1) the baseline visit.

- Informed Consent
- Pregnancy Test
- Urinalysis
- Medical History
- Post Void Residual Test
- Cough Stress Test
- 24-hour Pad Weight Test
- Medication Documentation
- Urinary Distress Index (UDI-6)
- Incontinence Impact Questionnaire (IIQ-7)
- Visual Analog Scale for Pain (VAS Pain)

5.2 Procedure Visit

The first surgical implant procedure after the subject is enrolled in the study is considered the index procedure. For newly implanted subjects a standard implant procedure is to be used as detailed in the Instructions for Use for Altis SIS or control product, as applicable. Implant procedure information will be collected as well as medication use during and after the procedure. Any deviation from the procedure should be identified on the appropriate procedure form and detailed on a study deviation form.

The subject will complete a VAS Pain questionnaire each day for the 3 days following their index procedure. The subject will be supplied with a postage paid return envelope to send the questionnaires back to the study site upon completion.

5.3 Follow-Up Visit Schedule

Data will be collected following the index procedure at 6 months, 12 months, 18 months, 24 months, and 36 months following the index procedure. Every attempt should be made to complete follow-up visits, however, if the subject cannot be seen in person, required questionnaires and pad weight testing kits should be mailed to the participant with a postage paid return envelope. If the follow-up visit cannot be completed within the visit window, the visit should still be completed as soon as possible and a study deviation form completed. All adverse events that are identified at any follow-up visit will be recorded on the appropriate adverse event form.

5.3.1 Follow-up Visits: 6, 12, 18, 24, and 36 Month

Subjects are required to return to the office for required follow-up visits. The following procedures will be performed at each follow-up visit:

- Post Void Residual Test
- Cough Stress Test
- 24-hour Pad Weight Test
- Medication Documentation
- Patient Global Impression of Improvement (PGI-I)
- Urinary Distress Index (UDI-6)
- Incontinence Impact Questionnaire-Short Form (IIQ-7)
- Surgical Satisfaction Questionnaire (SSQ-8) – 6 months only
- Visual Analog Scale for Pain (VAS Pain) – 6 months only
- Assessment of Adverse Events

5.3.2 Unscheduled Follow-up Visits

Unscheduled follow-up visits include adverse event assessment or adverse event follow-up visits. If an unscheduled visit occurs, the following items will be collected:

- Assessment of Adverse Events (captured on an Unscheduled eCRF and Adverse Event eCRF, as applicable)
- Assessment of any additional procedures (captured on Unscheduled eCRF)

Table 2 Follow-up Schedule and Windows

Follow-Up	Window Start	Target Day	Window End
6 Months (+ 21 days)	159 days	180 days	201 days
12 months (+ 42 days)	323 days	365 days	407 days
18 months (+ 42 days)	506 days	548 days	590 days
24 months (+ 42 days)	688 days	730 days	772 days
36 months (+ 42 days)	1053 days	1095 days	1137 days

5.4 Device Revisions and Explants

All device revisions/resurgeries including explants will be recorded.

Device Revision is defined as a surgical procedure to alleviate a problem associated with the implanted device after initial implant and/or removal and replacement with any mid-urethral sling.

Device Explant is defined as the removal of the Altis Single Incision Sling or the transobturator/retropubic sling.

If Altis SIS is removed for any reason, the device should be returned to Coloplast. The product should be handled as a bio-hazardous material and sent to:

Coloplast Manufacturing
Attn: Product Evaluation Dept
1601 West River Road North
Minneapolis MN 55411
Ref: Altis 522 Study

5.5 Randomization Procedure

There are no randomization procedures in this study.

5.6 Blinding

Study subjects and investigational study personnel are not blinded to study group assignment.

6 Identification and Description of Devices

6.1 Description of the Study Device

Altis SIS is a permanently implantable synthetic sling for the surgical treatment of SUI. Altis SIS is made from a knitted, monofilament polypropylene with low elasticity. This structure gives Altis SIS resistance to traction, allows tissue in-growth and facilitates positioning during surgery. Altis SIS is placed at the mid-urethra to treat SUI by providing a scaffold for tissue in-growth and support for stress events.

Altis SIS is sterile, single-use only synthetic sling with left and right introducer needles. The specialized introducers allow the physician to position anchors in the obturator foramen through a single vaginal incision. The introducers can only be used with Altis SIS and are indicated for single use.

6.2 Description of Coloplast Control Devices

Coloplast currently markets slings that may be part of the Control group consisting of transobturator or retropubic slings. Descriptions of these devices are provided.

6.2.1 Aris® Trans-Obturator Sling

Coloplast Aris Trans-Obturator sling is a permanent, synthetic sub-urethral sling. It is indicated for the surgical treatment of all types of stress urinary incontinence (SUI), for female stress urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency (ISD). Aris is made from knitted, monofilament polypropylene and has low elasticity. This structure gives Aris resistance to traction, allows tissue colonization and facilitates positioning during surgery.

The Aris sling is provided sterile and is for single-use only. The Aris sling is sterilized by ethylene oxide. Introducer Needles are available and intended to facilitate the placement of the Aris Trans-Obturator Sling.

6.2.2 Supris® Retropubic Sling System

The Supris sling is a permanent, synthetic sub-urethral sling that is provided with disposable introducer needles in the Supris Retropubic Sling System. It is indicated for the surgical treatment of all types of stress urinary incontinence (SUI), for female stress urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency (ISD).

Supris sling is made from knitted, monofilament polypropylene and has low elasticity. This structure gives the Supris sling resistance to traction, allows tissue colonization and facilitates positioning during surgery. The Supris sling is provided sterile and for single-use only. The Supris sling is sterilized by ethylene oxide. Sterile, single-use only, introducers are included in this system. The introducers are manufactured from polypropylene (handles) and medical grade stainless steel (Introducer Needles) and are sterilized by ethylene oxide. These introducers can only be used with Coloplast Supris sling.

6.3 Manufacturer

Coloplast A/S manufactures Altis SIS, Aris Trans-Obturator Sling, and the Supris Retropubic Sling.

6.4 Identification, Traceability and Labeling of the Devices

All devices are commercially available for use and will be labeled with a catalog and lot number. The catalog and lot number of each device used will be entered into the study database.

6.5 Intended Population for the Device

The study population will include adult female patients indicated for surgical treatment of stress urinary incontinence. All study candidates must provide written informed consent and be available for follow-up visits at an approved study site.

6.6 Handling and Training

Appropriate physician and site training will be required for study participation. Physicians new to using the slings and/or with less than 6 months of experience will be required to undergo surgical training for the study or Coloplast control device, which may include a cadaver lab, simulation training, or case proctoring by an experienced physician or by a Coloplast representative

7 Statistical Considerations

7.1 Analysis Populations

The Intent-to-Treat (ITT) analysis population consists of all subjects who have undergone a sling implant attempt for stress urinary incontinence for this study using either Altis SIS or a FDA cleared transobturator or retropubic sling. The ITT analysis population is the primary population for the assessment of all safety and effectiveness endpoints.

The per-protocol (PP) population includes all subjects in the ITT analysis population who meet all inclusion/exclusion criteria. The PP population will be used as a secondary (supplementary) analysis population to confirm and further substantiate the results of effectiveness endpoints based on the ITT analysis population.

7.2 General Analysis Principles

All analyses will be performed by a contracted statistician. Continuous variables will be summarized with means and standard deviations or as medians and interquartile ranges. Categorical variables will be summarized with the number and proportion of subjects in each category. Binary outcomes will be presented as proportions with corresponding 95% asymptotic confidence limits.

At a minimum, primary and secondary effectiveness endpoints will also be analyzed for subjects who had baseline urinary leakage of ≥4g as assessed by the 24-hour pad weight. Other subgroup analyses may be performed as appropriate for the question of interest.

All statistical analyses will be conducted using SAS version 9.3 or later (SAS Institute Inc., Cary, NC) or R version 2.14 or later (R Development Core Team, 2012).

7.3 Missing Data

The number and proportion of missing values at each observation period will be reported along with the reason for missing data, if known. Specific missing data handling procedures for each of the powered primary and secondary endpoints are presented in the endpoint analysis sections below (7.4-7.6). No missing data handling procedures for the other secondary endpoints are pre-defined.

7.4 Analysis of Primary Effectiveness Endpoint

The number and proportion of patients meeting the primary endpoint will be tabulated for each treatment group at 6 months. Non-inferiority will be assessed using a normal approximation test (Z-test) for a difference in binomial proportion. Non-inferiority will be achieved if the upper limit of the 95% confidence interval for the difference in proportions (Control – Treatment) is less than 0.15.

The null and alternative hypothesis for this test will be as follows:

Ho: $\pi_c - \pi_T \geq 0.15$

Ha: $\pi_c - \pi_T < 0.15$

where π_c is the proportion of subjects in the control group meeting the primary effectiveness endpoint and π_T is the proportion of subjects in the treatment group meeting the primary effectiveness endpoint and 0.15 is the non-inferiority margin.

Handling of Missing Data

The primary analysis of the primary effectiveness endpoint will include all available data and 'presumed failures' from the ITT analysis population. Presumed failures are defined as subjects with missing data where it is known that the cause of the data loss is either related to an adverse event (including death) or to a device failure. Subjects with missing data for other reasons will be ignored in the primary analysis, but will be included in all sensitivity analyses. The sensitivity analyses for the primary effectiveness endpoint will include best case, worst case and tipping point analysis.

7.5 Analysis of Primary Safety Endpoint

The number and proportion of subjects experiencing device- and/or procedure-related serious adverse events will be tabulated for each study group. Non-inferiority at 36 months will be calculated using a normal approximation test (Z-test) for a difference in binomial proportion with the following null and alternative hypotheses:

H_0: $\pi_c - \pi_T \leq -0.10$

H_A: $\pi_c - \pi_T > -0.10$

where πc is the proportion of patients who have the primary safety endpoint during follow-up in the control group and π_T is the proportion of patients who have the primary safety endpoint during follow-up in the treatment group.

Handling of Missing Data

The primary analysis of this endpoint will include all available data from the ITT analysis population. Subjects that have not experienced a device- and/or procedure-related serious adverse event and who have missing data at 36 months will be assumed to be free of such an adverse event. However, the potential impact on the endpoint inference of all such subjects will be assessed via various sensitivity analyses that include best case, worst case and tipping point

analysis. In addition, a Kaplan-Meier product limit analysis that right censors subjects lost to follow-up will be conducted to further understand the potential impact of subject loss.

7.6 Analysis of Powered Secondary Safety Endpoints

7.6.1 Secondary Safety Endpoint

The number and proportion of subjects experiencing any device- and/or procedure-related adverse event will be tabulated for each group. Non-inferiority at 36 months will be calculated using a normal approximation test (Z-test) for a difference in binomial proportion with the following null and alternative hypotheses:

H_0: $\pi_c - \pi_T \leq -0.15$

H_A: $\pi_c - \pi_T > -0.15$

where πc is the proportion of patients who have the secondary safety endpoint during follow-up in the control group and π_T is the proportion of patients who have the secondary safety endpoint during follow-up in the treatment group.

Handling of Missing Data

The primary analysis of this endpoint will include all available data from the ITT analysis population. Subjects that have not experienced a device- and/or procedure-related adverse event and who have missing data at 36 months will be assumed to be free of such an adverse event. However, the potential impact on the endpoint inference of all such subjects will be assessed via various sensitivity analyses that includes best case, worst case and tipping point analysis. In addition, a Kaplan-Meier product limit analysis that right censors subjects lost to follow-up will be conducted to further understand the potential impact of subject loss.

7.6.2 Revision/Resurgery

The number and proportion of subjects experiencing revision and/or resurgery will be tabulated for each treatment group. Non-inferiority at 36 months will be calculated using a normal approximation test (Z-test) for a difference in binomial proportion with the following null and alternative hypotheses:

H_0: $\pi_c - \pi_T \leq -0.10$

H_A: $\pi_c - \pi_T > -0.10$

where πc is the proportion of patients who have the revision/resurgery endpoint during follow-up in the control group and π_T is the proportion of patients who have the revision/resurgery endpoint during follow-up in the treatment group.

Handling of Missing Data

The primary analysis of this endpoint will include all available data from the ITT analysis population. Subjects that have not experienced a revision/resurgery and who have missing data at 36 months will be assumed to be free of such an event. However, the potential impact on the

endpoint inference of all such subjects will be assessed via various sensitivity analyses that includes best case, worst case and tipping point analysis. In addition, a Kaplan-Meier product limit analysis that right censors subjects lost to follow-up will be conducted to further understand the potential impact of subject loss.

7.7 Additional Secondary Endpoints

7.7.1 24-Hour Pad Weight

Differences in 24-hour Pad Weight will be assessed at 6 months, 12 months, 18 months, 24 months, and 36 months.

7.7.2 Quality of Life

Change in Quality of life (QoL) scores from baseline to follow-up will be summarized at each visit and for the treatment and control group for all QoL questionnaires. The treatment group will be compared to the control group using a linear model that is fit with generalized estimating equation methodology to control for correlation due to repeated measurements on each subject. Differences between the treatment group and the control group will be assessed at each visit and overall.

For subjects with revision or resurgery within 36 months of the index surgery, QoL assessments following revision or resurgery will be evaluated.

7.7.3 Adverse events

All adverse events will be summarized at 6 months, 12 months, 18 months, 24 months, and 36 months. The proportions of subjects with events will be reported as well as Kaplan-Meier event rates at the time points of interest.

For subjects with revision or resurgery within 36 months of the index surgery the rates of adverse events peri-procedural (within 30 days) following revision or resurgery will be assessed.

7.8 Propensity Analysis

In addition to the primary and secondary analyses of the effectiveness and safety endpoints, a propensity analysis will be conducted to address the effect of potential confounding variables on our conclusion. Risk factors that will be analyzed are outlined in Section 3.3.5.

For this analysis, a logistic regression model will be used to calculate the probability of treatment assignment given the covariates listed above (i.e., the propensity score). The covariates will not be grouped, resulting in one propensity score for each subject. The propensity score will be used in an adjusted regression model for each primary endpoint. A logistic regression model will be used for the primary effectiveness and safety endpoints.

7.9 Sample Size

7.9.1 Final Sample Size

Sample size was calculated to assess non-inferiority of the primary effectiveness endpoint and primary safety endpoint at 80% power with a type-I error rate of 0.05 for each primary endpoint analysis. The sample size calculations were conducted in PASS 16.

The final sample size was determined to be the maximum of these sample size calculations for the primary effectiveness and safety endpoints. This requires 328 total subjects.

7.9.2 Sample Size Estimation for Primary Effectiveness Endpoint

The sample size for the primary effectiveness endpoint was calculated to assess non-inferiority. We assume 20% loss to follow-up at the end of the study, 6 month event rates of 75% in Altis group and 75% in control group with a non-inferiority margin of 15%.

Assuming an equal allocation, a minimum of 131 evaluable subjects per treatment arm are required to power this endpoint to the nominal 80% level. Accounting for 20% loss to follow-up, the minimum number of implanted subjects required is 164 in each arm for a total of 328 subjects.

7.9.3 Sample Size Estimation for Primary Safety Endpoint

The sample size for the primary safety endpoint was calculated to detect a non-inferiority limit of 10% assuming an underlying rate of device and procedure related serious adverse event of 10% in each group with 80% power and assuming 20% loss to follow-up by 36 months. The rate of serious device and/or procedure related adverse events in the IDE study was 2.7% (3/113) through 12 months of follow-up. A conservative estimate of 10% was used for the purpose of sample size estimation to account for the additional follow-up time and to ensure adequate power. The sample size required to maintain 80% power is 178 subjects per study group accounting for 20% attrition for a total of 356 subjects.

7.9.4 Sample Size Estimation for Powered Secondary Safety Endpoints

Device- and/or Procedure-Related Adverse Events

The overall rate of device or procedure related adverse events in the IDE study was 14%. A conservative estimate of 20% is chosen to account for the additional follow-up time. Assuming an underlying rate of any device and/or procedure related adverse event of 20% in each group, a sample size of 112 subjects per study group, for a total of 224 subjects, is required to power for the assessment of the secondary safety endpoint. Accounting for up to 20% attrition, 140 subjects per study group would need to be implanted, for a total of 280 subjects.

Revision/Resurgery

Because the rates of revision/resurgery are expected to be less than the rates for the primary safety endpoint the study is adequately powered for this objective as this endpoint utilizes the same non-inferiority limit as the primary safety endpoint.

7.9.5 Level of Significance and Power

All tests of significance will be performed at the two-sided 0.05 significance level (one-sided 0.025). As both the primary effectiveness and safety objectives must be met for study success, no adjustment for multiplicity is required. Additionally, the secondary safety endpoints for 1) device and/or procedure related adverse events, and 2) revision or resurgery, will be tested hierarchically in the order presented in the event the primary safety objective is met. Therefore no adjustment for multiplicity is required.

7.9.6 Drop-out

Drop-out rates are expected to be uniform over time and not to exceed 20% of the original sample at the conclusion of the study. All sample size calculations were adjusted for the expected rate of drop-out and loss to follow-up.

7.10 Interim Analysis

No formal interim analyses are planned. Interim (or annual, as required) post-market surveillance reports will be submitted to FDA. These reports will include all the required elements, and summary and interpretation of study results. For the progress reports, endpoint results will be summarized as appropriate (e.g., via counts and percentages), however, no statistical testing will be performed and no p-values will be provided until data collection for this endpoint has been concluded.

8 Data Quality Assurance

8.1 Electronic Data Capture

The study will use a secure 21 CFR Part 11 compliant Electronic Data Capture (EDC) system to collect and store data. The electronic case report forms (eCRFs) are designed to accommodate specific features of study design and will be used to capture data. All data will be entered in the EDC system.

Paper QoL questionnaires will be provided to study subjects at each visit and will be entered in the EDC system after completion by study staff delegated and trained to perform eCRF completion. The principal investigator will review all eCRFs for completeness and accuracy and will electronically sign the forms to confirm approval.

8.2 Monitoring Plan

It is the responsibility of Coloplast to ensure that proper monitoring of this study is conducted according to the Monitoring Plan. Appropriately trained personnel consisting of in-house and/or contracted monitors will perform site monitoring to ensure that the study is conducted in accordance with the signed Investigator Agreement and applicable regulations. The monitor must be allowed access to site and study subject files. The monitor will review subject records, consent forms, regulatory and study management documents to assess the accuracy of recorded data, study progress, and regulatory compliance. The principal investigator is ultimately responsible for compliance and will work with delegated research staff and the monitor to resolve all data queries and monitoring action items. Resolution of these items and completion of assigned tasks will be documented by the monitor or clinical designee. Failure to obtain compliance of monitoring

findings may result in suspension of enrollment until compliance is obtained. The frequency of monitoring visits will be based on enrollment rates, duration of the study, site compliance, and data quality at each investigative site.

8.3 Audits

Audits of the study may be conducted by the sponsor, regulatory agencies or a third party designated by the sponsor to evaluate compliance with the protocol, investigator agreement, and written procedures. These audits may cover all involved parties, systems, and facilities supporting the conduct of the study and are independent of, and separate from, routine monitoring functions.

9 Ethical Considerations, Device and Clinical Study Risks and Benefits

The clinical study will be conducted in accordance with current law and applicable standards (see Section 13). The rights, safety and well-being of human subjects shall prevail over interest of science and society.

9.1 Informed Consent Process

Written informed consent must be obtained from all subjects participating in the study following detailed written and verbal briefing and prior to completion of any study related activities according to IRB regulations. Each subject will be fully informed about the aim of the study, procedures, potential risks or inconveniences and/or expected benefits. Subjects will be provided sufficient time to ask questions before deciding on whether or not to participate in the study. Subjects will be informed that their participation is voluntary and that they may leave the study at any time, without influencing their further treatment.

The informed consent signature form includes the signatures of the subject (or subject's legal representative) and the date. A copy will be provided to the subject and the consent process should be documented in the subject's medical record.

If new information becomes available that can significantly affect a subject's future health and medical care, the information will be provided to the subjects in written form. The Clinical Trial Manager is responsible for producing the written information and providing it to investigators who will provide it to the subjects. If applicable, all affected subjects will be asked to confirm their continued, informed consent in writing.

9.2 Sample Informed Consent Form

A sample informed consent document suitable for use in this study, including the elements of informed consent in conformance with 21 CFR Part 50 will be provided by the sponsor. Changes to this document must include the essential elements of informed consent and should be approved by the sponsor prior to IRB/EC review. Subjects must be presented with the most current IRB/EC approved version of the consent form.

9.3 Institutional Review Board/Ethics Committee

This protocol and/or other relevant study documents must be submitted to the appropriate local or central IRB/EC. Written approval must be obtained before commencement of the study.

Approval obtained from the IRB/EC should document the version of the protocol and consent that is being approved. All amendments to the protocol will also be submitted to the same IRB/EC.

9.4 Data Protection

All information collected during the course of this study will be kept strictly confidential. Any information that could identify a subject will remain with the investigator where it will be archived with study documents. Subjects will remain anonymous for the purposes of data analysis. Data collected for the purposes of this study should be made available for Coloplast or designated contracted monitors at all monitoring visits. A contracted statistician will conduct data analysis and provide data tables to the sponsor.

9.5 Risks and Benefits

Subjects participating in the study will be exposed to the same operative and post-operative risks as patients undergoing surgical procedures for single-incision or traditional full length sling devices not associated with study participation. Risks can be minimized through the use of strict aseptic technique, compliance with this protocol and technical implant procedures, adherence to the guidelines for subject selection, close monitoring of the subject during implant and follow-up, and by promptly supplying the sponsor with all pertinent information in a timely manner. Risks to study subjects will be further minimized by providing appropriate training to study investigators new to using Coloplast products and by study monitoring during the course of this clinical study.

As with any surgical treatment for incontinence, there is always the risk that the treatment will not be successful or that incontinence will recur. There is a risk that, if the mesh causes problems, (e.g. extrusion - defined as mesh exposure in the vagina, pain, or infection), removal of the mesh may be necessary, and complete removal of the mesh may not be possible. Problems may persist, with or without complete mesh removal. These residual risks will be mitigated by pre-implant patient education, informed consent, selection of experienced surgeons for participation in the study, appropriate patient selection, appropriate device-implant training for physicians new to using Coloplast slings, and use of good medical and surgical technique to avoid known and potential causes of mesh problems.

Anticipated risks of use of the study device are listed in Section 14. Potential risks of participation in the study include, but are not limited to:

- Inadvertent sharing of study subject information that is intended to be private

Potential benefits of the study device include, but are not limited to:

- Cure or improvement of stress urinary incontinence
- Improvement of quality of life

10 Data Management

Data will be captured in a database using eCRFs to accommodate specific features of the study design and will be used to capture study specific data. Training will be provided for all study personnel entering data into the database prior to being given access to the database.

Edit checks will be created for quality control. Data will be subject to initial inspection for omitted data, data inconsistencies, and deviations. The resolution of any inconsistencies will be resolved through data queries. The site will be asked to review and respond to the data queries.

Study staff delegated by the principal investigator may complete the eCRF; however, the principal investigator will review all eCRFs for completeness and will electronically sign the forms.

11 Amendments to the Clinical Study Plan

Changes to the Clinical Study Plan are not permitted without Sponsor approval. Any significant changes to the study plan must be:

- Agreed to by the Principal Investigator
- Registered in the Change Log.
- Approved by the IRB/EC prior to implementation (if applicable).
- Approved by the appropriate regulatory authorities prior to implementation (if applicable).

12 Clinical Study Deviations

A clinical study deviation is defined as an event where the clinical investigator or site personnel did not conduct the study in accordance to the Clinical Study Plan or the investigator agreement. No deviations are allowed from the study protocol unless under emergency circumstances and to protect the rights, safety and well-being of the subject(s). All deviations must be documented. Deviations must be reported to the sponsor and to the local IRB/EC per the specific reporting requirements. In the case of continued or repeated deviations affecting subject rights, safety and well-being, the sponsor may terminate the PI from further participation in the study.

13 Statement of Compliance

The clinical study is conducted, (as applicable to the geographic region of each individual clinical site) in accordance with:

- CFR Title 21: Part 11 – Electronic Records; Electronic Signatures
- CFR Title 21: Part 50 – Protection of Human Subjects
- CFR Title 21: Part 54 – Financial Disclosures by Clinical Investigators
- CFR Title 21: Part 56 – Institutional Review Boards
- ISO 14155:2011 (E) (as regionally applicable)
- Ethical principles that have their origin in the Declaration of Helsinki, 1964, Last amended at the 59th WMA General Assembly, Seoul, October 2008.
- ICH Guidelines for Good Clinical Practice (E6 or E6 R1, as regionally applicable)
- Guidance for Industry Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects, October 2009
- Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs – Improving Human Subject Protection, January 2009

14 Adverse Events, Serious Adverse Events, and Device Deficiencies

14.1 Adverse Event/Complication Classification

Collection of Adverse Events will begin at the time the first incision is made for the index surgical procedure and will continue until the subject's study participation is complete. The investigator will be asked to assess the relationship of the event to the implanted study product, the implant study procedure, and the presence or performance of the mesh itself for each adverse event reported. Serious and non-serious adverse events will be collected and reported for this study.

The principal investigator will ensure that adequate medical care is provided to all subjects experiencing an adverse event during or after participation in the clinical investigation. Any ongoing adverse events must be assessed on an ongoing basis to determine resolution.

The current status of all ongoing adverse events is documented at the time of site close-out. The resolution date will be recorded on an adverse event eCRF.

14.1.1 Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including abnormal laboratory findings) that may occur in subjects, users or other parties, whether or not it is related to the medical device(s), or the procedure's involved. Potential adverse events include but are not limited to:

- Erosion - Defined as movement of mesh into any other organ or body plane.
- Exposure – Defined as a condition of displaying, revealing, exhibiting or making accessible (e.g. vaginal mesh visualized through separated vaginal epithelium)
- Extrusion - Defined as passage gradually out of a body structure or tissue.
- Sling Migration - Defined as movement from the original implanted mid-urethral site.
- Transient or permanent urinary retention/obstruction.
- Foreign body reaction - Defined as absence of tissue in-growth resulting in the presence of granulation tissue.
- Reaction from anesthesia (respiratory failure, allergic reaction, thromboembolic event)
- Vaginal discharge
- Abscess
- Pain
- Delayed wound healing
- De novo or worsening urgency/overactive bladder
- De novo or worsening dyspareunia
- Genital/pelvic pain
- Hematoma and/or hemorrhage
- Infection
- Inflammation
- Paresthesia (genital)
- Scar tissue formation
- Bladder perforation
- Urethral perforation
- Bowel perforation
- Voiding dysfunction
- Worsening incontinence

- Urethral obstruction
- Vascular injury
- Nerve injury
- Urinary tract infection

14.1.2 Serious Adverse Events

A serious adverse event (SAE) is an adverse event that led to:

- Life Threatening: The participant was at imminent risk of dying at the time of the adverse event.
- Permanent Impairment: An adverse event that resulted in permanent impairment of a body function or permanent damage to a body structure.
- Necessitates Intervention: An adverse event that resulted in a condition that necessitates medical or surgical intervention to preclude permanent impairment of a body function or damage to a body structure.
- Hospitalization/Prolongs Hospitalization: Requires inpatient hospitalization or prolongs an existing hospitalization. Planned hospitalization for a pre-existing condition is not considered a serious adverse event.
- NOTE: Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
- Results in Death: An adverse event that results in the participant's death.

14.1.3 Unanticipated Adverse Device Effect (UADE)

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 study plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

14.1.4 Adverse Event Severity Classification and Device Causality

The investigator will classify adverse events by relatedness to the device or procedure, as follows:

A **device related** adverse event is an event that results from the presence or performance of the device. In this study, the device is the Altis Sling or control device (transobturator or retropubic sling). Device related events can include, but are not limited to**:** erosion, extrusion, urinary retention, sling migration and foreign body reaction.

A **procedure related** adverse event is an adverse event that occurs due to the implant procedure**.**

The investigator will classify adverse events by severity, as follows:

A **Mild** event is an adverse event that is reported without any action(s) taken.

A **Moderate** event is an adverse event that is not severe, but requires action.

A **Severe** event is an adverse event that results in a subject's hospitalization, or their hospitalization is unduly prolonged because of potential disability or danger to life, or an intervention has been necessitated, or the event is terminal.

14.2 Device Deficiency and Technical Observations

A device deficiency refers to the inadequacy of the medical device with respect to its identity, quality, durability, reliability, safety or performance. This includes malfunctions, misuse or user errors and inadequate labeling.

A technical observation is a failure or malfunction of the device, or a device/system functioning not according to the design intent that does not result in subject symptoms.

Examples of device deficiencies and/or technical observations include, but are not limited to: mechanical failure of the mesh, mesh does not withstand insertion or in use of forces when inserted, defect in mesh when removed from package.

15 Adverse Event Review

15.1 Clinical Events Committee

A clinical events committee (CEC) will be used to adjudicate device and procedure related serious adverse events. Additional adverse events may be specified for CEC adjudication throughout the study. The CEC adjudication of adverse events will be used for data analysis. The CEC will be made up of a group of independent physicians specializing in the treatment of SUI. Responsibilities of the CEC may include, but are not limited to reviewing individual adverse events to determine severity and relationship to the study device and/or procedure.

16 Reporting and Timelines

16.1 Investigator Reporting Responsibilities

In addition to the requirements stated in the investigator agreement, the investigator is responsible for the preparation (review and signature) and retention of the records cited below. All of the records below, with the exception of case history records, should be kept in the Investigator Site File (i.e., study binder). The following records are subject to inspection and must be retained according to the agreed upon timeframe in the investigator agreement (or longer, if local law or hospital administration requires) after study closure.

- All substantial correspondence that pertains to the conduct of the study. Any correspondence describing rationale for decisions made affecting subject safety and privacy or data collection and reporting is considered substantial correspondence
- Subject's case history records including: signed informed consent/applicable privacy protection authorization form; observations of adverse events/adverse device effects; medical history; implant and follow-up data; documentation of the dates and rationale for any deviation from the protocol
- Signed Investigator Agreement and current curriculum vitae (CV)
- Ethics committee documentation
- Site personnel training records

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all eCRFs, adverse events (reported per the country-specific collection requirements), deaths, and any deviations from the study plan. These reports are also subject to inspection and to the retention requirements described above for investigator records. If any action is taken by an IRB/EC with respect to the clinical study, the information must be forwarded to the Sponsor.

Table 3 Investigator Reporting Requirements

Report	Submit To	Description/ Constraints
AE – Adverse Event	Sponsor, IRB/EC (per local requirements)	Any adverse event must be reported as soon as possible via the EDC system
SADE - Serious Adverse Device Effect	Sponsor, IRB/EC (per local requirements)	Any adverse device effect must be no later than 24 hours or the next business day after first learning of the event
SAE-Serious Adverse Event	Sponsor, IRB/EC (per local requirements)	Any serious adverse event must be reported no later than 24 hours or the next business day after first learning of the event
UADE-Unanticipated Adverse Device Effect	Sponsor, IRB/EC	If an unforeseen complication is determined to be a Serious, device related, unanticipated AE then the investigator's report must be submitted as soon as possible but no later than within 24 hours or the next business day after the investigator first learns of the event
Withdrawal of IRB/EC approval	Sponsor	Notification within 24 hours or next business day
Progress Report (US only)	Sponsor IRBs	The investigator must submit this report annually, unless IRB requires more frequent submissions
Deviation from study Plan	Sponsor IRBs/ECs	Any deviation from the study plan must be reported to the Sponsor via the EDC system and reviewing local IRB/EC per local reporting requirements
Failure to obtain informed consent	Sponsor IRBs/ECs	In the US, the investigator must submit notification within 5 working days after device use.
Final report (US only)	Sponsor IRBs	This report must be submitted within 3 months of study completion or termination.
Device deficiency or technical observation	Sponsor, IRB/ECs per local reporting requirements	Notification within 24 hours or the next business day.

All adverse events listed above must be reported using the relevant adverse event/serious adverse event/device deficiency eCRF in the EDC system.

Source documentation for adverse events, including medical history, operative data, follow-up visit notes, any hospitalization records may be requested by Coloplast. If requested, please submit redacted/de-identified source documentation with the subject ID to:

Name: Coloplast Clinical Department
Address: 1601 West River Road N
City, State: Minneapolis, MN 55406
Phone: 763-248-5744
Fax: 612-337-7910
Email: uskve@coloplast.com

Table 4 Coloplast Reporting Requirements

Report	Submit To	Description
UADE-Unanticipated Adverse Device Effect	Investigators IRBs/ECs as applicable, FDA	Notification within 10 working days after the sponsor first learns of the effect.
Withdrawal of IRB/local ethics committee approval	Investigators IRBs/ECs, as applicable FDA	In the US, Notification within 5 working days.
Recall and device disposition	Investigators IRBs ECs, as applicable FDA	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices.
Progress Reports (If required by local law)	Investigators IRBs/ECs, as applicable FDA	Every 6 months for the first 2 years, then annually after.
Final report	Investigators IRBs/ECs, as applicable FDA	Coloplast will notify the investigators of the completion or termination of the study. A final report will be submitted to the investigators and IRBs/MECs within three months after completion or termination of this study. In Europe, the investigator must confirm the receipt of the final report composed by Coloplast (and confirm agreement with the study results)

16.2 Records Retention

All study site files and the investigation database, must be archived for a minimum period of 2 years following the date of study closure as determined by Coloplast .

The monitor is responsible for informing the investigator and the trial manager if this period should be longer for their sites according to local regulations.

17 Suspension or Premature Termination of the Clinical Study

The sponsor may suspend or prematurely terminate the clinical study at any time for significant and documented reasons. Significant reasons include but are not limited to, safety concerns, failure to meet enrollment goals, or change in market conditions, such as, significant decrease in mesh-based transvaginal procedures for stress urinary incontinence repair.

If a suspicion relating to an unacceptable risk to subjects arises during the clinical study, the sponsor may suspend the study while the risk is assessed. The sponsor will terminate the study if an unacceptable risk is confirmed. The sponsor must ensure that the premature termination is

justified in writing and that the regulatory authorities and relevant IRB/EC(s) are informed promptly.

In the event the clinical study is terminated, treated subjects (having undergone surgical intervention) should be followed per protocol through the completion of their 36 month follow-up visit. In addition, IRBs/ECs will be notified of the decision to terminate the study.

After the follow-up requirements are met, subjects will be notified that their participation in the clinical study is complete. Following the completion of study participation, subjects should be seen per local standard of care.

Adverse events that occur following study termination will be reported to Coloplast via the complaint management system and will be processed per Coloplast complaint handling procedures and reported to Regulatory Authorities per local reporting requirements.

18 Suspension or Premature Termination of a Study Site

If monitoring or auditing of a clinical study site identifies serious and/or repeated deviations, and compliance cannot be secured in a timely manner, the sponsor may suspend or terminate the study site. All reasonable efforts will be made by Coloplast in conjunction with the Principal Investigator to secure compliance and prevent future occurrences. The sponsor or investigator will inform the regulatory authorities as appropriate and notify the IRB/EC about the termination of the site.

19 Publication policy

Coloplast will form a publication committee that includes at least two participating investigators. The committee will develop a collaborative publication strategy.

20 References

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Attachment 1 Change Log

VERSION NUMBER	ISSUED BY (INITIALS)	COMMENTS (MAJOR CHANGES SINCE LAST REVISION)	PAGE NUMBERS AFFECTED
1.0	USDKL	Document established	N/A
2.0	USLKR	The registered trademark symbol, designated by ® was added after Altis.	Page 1, Study Title.
2.0	USLKR	The version of the protocol was updated to 2.0 and the date of April 22, 2014.	Page 1, Cover page and footer for all pages.
2.0	USLKR	Removed from study population, subjects who were enrolled in the Altis SIS FDA Investigation Device Exception (IDE) Study. All research sites that participated in the IDE study will not take part in the 522 study.	Page 6, Synopsis of Clinical Study. Page 16, Section 3.2.2 Site and Investigator Selection. Page 19 Section 3.4 Subjects. Page 20 Section 3.5, Subject Recruitment and Enrollment.
2.0	USLKR	Added to primary and secondary effectiveness endpoints “or are considered dry (pad weight ≤4.0 grams) at 6 months” using the 24 hour pad weight test per Reference Number 9 in Section 20.	Page 6, Primary Effectiveness Endpoints. Page 7, Secondary Effectiveness Endpoint. Page 18, Section 3.3.2 Primary Effectiveness Endpoints and Section 3.3.4, Secondary Effectiveness Endpoint.
2.0	USLKR	Added 2 questionnaires (Surgical Satisfaction Questionnaire and Visual Analog Scale for Pain) for quality of life assessment.	Page 7, Secondary Effectiveness Endpoint. Page 18, Section 3.3.4 Secondary Effectiveness Endpoint.
2.0	USLKR	Stress or urge predominance will be determined using the MESA Incontinence questionnaire.	Page 7, Exclusion Criteria for Subject Selection. Page 19, Section 3.4.2 Exclusion criteria for subject selection.
2.0	USLKR	Removed the word “consistently” and clarified the number of occasions a PVR of >100 would need to be obtained to meet the exclusion criterion.to reduce ambiguity.	Page 7, Exclusion Criteria for Subject Selection, Number 8. Page 19 Section 3.4.2, Number 8.
2.0	USLKR	Added MESA, SSQ, and VAS to the List of Abbreviations.	Pages 9 and 10. List of Abbreviations.
2.0	USLKR	Clarified maximum patient enrollment at each site to attempting to implant no more than 20% of subjects in each respective arm without prior approval from Coloplast.	Page 16, Section 3.2.1 General.
2.0	USLKR	Updated Flow-Chart. Inclusion exclusion criteria can be assessed through standard of care exams. Therefore, informed consent process will occur after subject meets inclusion/exclusion criteria.	Page 17. Figure 1: Overall Study Design Flow-Chart.
2.0	USLKR	Updated the abbreviation for Urogenital Distress Inventory to “UDI-6.”	Page 18, Section 3.3.4 Secondary Effectiveness Endpoint.
2.0	USLKR	Removed the specification of “70 +” after “Age” to describe the propensity analysis that will be conducted.	Page 18, Section 3.3.5 Risk Factors.

VERSION NUMBER	ISSUED BY (INITIALS)	COMMENTS (MAJOR CHANGES SINCE LAST REVISION)	PAGE NUMBERS AFFECTED
2.0	USLKR	Corrected typographical error; in the word “end.”	Page 20 Section 3.7, Subject withdrawal criteria
2.0	USLKR	Added “an Unscheduled Visit and Adverse Event eCRF” to describe where an adverse event assessment or adverse event follow-up will be recorded.	Page 21 Section 5, Paragraph three. Page 22, Section 5.3.2.
2.0	USLKR	Added column for Unscheduled Visit and collection of Medications, Surgical Satisfaction Questionnaires (SSQ-8), and Visual Analog Scale for Pain (VAS Pain). Also added collection of cystoscopy at the procedure visit.	Page 21 Table 1 Data Collection Schedule. Page 22, Section 5.1 and 5.2. Page 23, Section 5.3.1.
2.0	USLKR	Added Table Footnote 4, “Any procedures performed relevant to the continence state of the subject should be documented on the follow-up form (e.g. PVR, urinalysis, or CST testing).” Added Table footnote 5 “It is recommended that subjects complete pad weight testing within ± 1 month of the scheduled visit.” Added Table footnote 6 “The VAS Pain questionnaire will be completed by subjects at baseline and each day for the first 3 days following their index procedure, and at their 6 month follow-up visit.”	Page 21 and 22. Table 1 Data Collection Schedule. Page 21, Section 5.1, 5.2, and 5.3.1.
2.0	USLKR	Clarified CRFs to be used when an unscheduled visit occurs. Assessment of AEs will be captured on an Unscheduled eCRF and Adverse Event eCRF, as applicable. The assessment of any additional procedures will be captured on an Unscheduled eCRF.	Page 23, Section 5.3.2 Unscheduled Follow-Up Visits
2.0	USLKR	Clarified that the description of the control devices was for Coloplast products.	Page 24, Section 6.2 Description of Control Devices.
2.0	USLKR	Replaced the trademark symbol ™ after Aris and Supris with the registered trademark symbol, designated by ®.	Page 24 Section 6.2.1 Aris Trans-Obturator Sling and Page 25, 6.2.2 Supris Retropubic Sling System.
2.0	USLKR	Added that physicians new to using slings and/or with less than 6 months of experience will be required to complete the training listed.	Page 25 Section 6.6 Handling and Training.
2.0	USLKR	Revised analysis population to subjects who have undergone a sling implant attempt for stress urinary incontinence and removed subjects who were part of the IDE study.	Page 25 Section 7.1. Analysis Population.
2.0	USLKR	Revised who will perform analyses to a contracted statistician.	Page 26, Section 7.3 General Analysis Principles. Page 31 Section 9.4 Data Protection.
2.0	USLKR	Deleted references to the IDE study population since this population has been excluded from this study.	Page 26 Section 7.4 Missing Data.
2.0	USLKR	Deleted description of imputation analysis for IDE cohort.	Page 27 Section 7.8.1 24-Hour Pad Weight Test. Page 27 Section 7.8.2 Quality of Life.
2.0	USLKR	Deleted Section 7.12 Deviation from the Statistical Plan as this applies to the Statistical Plan and not the protocol.	Page 30 Section 7.12 Deviation from the Statistical Plan.
2.0	USLKR	Added that the study will be conducted according to the Monitoring Plan and that in-house and/or contracted monitors will be utilized. Deleted the sentence on how data clarifications and monitoring action items will be documented.	Pages 30, Section 8.2 Monitoring Plan.

VERSION NUMBER	ISSUED BY (INITIALS)	COMMENTS (MAJOR CHANGES SINCE LAST REVISION)	PAGE NUMBERS AFFECTED
		Added that a "clinical designee" may document resolution of data queries and monitoring action items.	
2.0	USLKR	Added "regulatory agencies" as body that may conduct study audits.	Page 30, Section 8.3 Audits.
2.0	USLKR	Added that informed consent process must follow IRB regulations. Deleted sentence in third paragraph regarding if new information becomes available, the sponsor will notify investigators as the next sentence provides more clarity as to what "new information" means.	Page 31, Section 9.1 Informed Consent Process.
2.0	USLKR	Changed "and" in first sentence to "or." Removed "local" in front of IRB/EC.	Page 31, Section 9.3 Institutional Review Board/Ethics Committee.
2.0	USLKR	Added "or designated contracted monitors" to people who would review data during monitoring visits.	Page 31, Section 9.4 Data Protection.
2.0	USLKR	Clarified that risks to study subjects will be minimized by providing training to investigators "new to using the Coloplast products."	Page 32, Section 9.5 Paragraph one and two.
2.0	USLKR	Modified the example of a risk to "(e.g. extrusion defined as mesh exposure in the vagina, pain, or infection.)"	Page 32, Section 9.5 Paragraph two.
2.0	USLKR	Deleted the sentence, "There are no known direct benefits to study subjects, individuals, or communities through participation in this study."	Page 32, Section 9.5, Paragraph three.
2.0	USLKR	Deleted part of a sentence describing study deviations "which may affect the rights, safety, and well-being of study subjects, the scientific soundness of the plan, validity of the data, or is non-compliant with applicable regulations.	Page 33, Section 12 Clinical Study Deviations.
2.0	USLKR	Regarding serious and non-serious adverse events, the following was deleted, "that are deemed to be device or procedure related by the Principal Investigator.	Page 33, Section 14.1 Adverse Event/Complication Classification.
2.0	USLKR	Deleted "Any ongoing adverse events must be assessed on an ongoing basis to determine resolution.	Page 33, Section 14.1 Adverse Event/Complication Classification
2.0	USLKR	Added that "The CEC adjudication of adverse events will be used for data analysis."	Page 36, Section 15.1 Clinical Events Committee
2.0	USLKR	Changed the number of years that study records must be archived to "2 years following the date of study closure as determined by Coloplast" and deleted "after the final clinical study report has been signed.	Page 39, Section 16.2 Records Retention.
2.0	USLKR	Deleted the word "prolapse" and inserted "stress urinary incontinence."	Page 39, Section 17 Suspension or Premature Termination of the Clinical Study.
2.1	USLKR	Updated the version and date of the protocol to 2.1 and September 10, 2014	Cover page
2.1	USLKR	Deleted "…or are considered dry (pad weight ≤ 4.0 grams)…" from the primary effectiveness endpoint	Page 6 of the Synopsis and page 18 in Section 3.3.2 Primary Effectiveness Endpoint
2.1	USLKR	Deleted "…or are considered dry (pad weight ≤ 4.0 grams)…" from the secondary effectiveness endpoint so it now reads "Observed effectiveness defined as a reduction from baseline in 24 hour pad weight of at least 50% at 12 months, 18 months, 24 months, and 36 months."	Page 7 of the Synopsis and page 18 in Section 3.3.4 Secondary Effectiveness Endpoint

VERSION NUMBER	ISSUED BY (INITIALS)	COMMENTS (MAJOR CHANGES SINCE LAST REVISION)	PAGE NUMBERS AFFECTED
2.1	USLKR	Added a new secondary effectiveness endpoint, "Observed effectiveness for subjects considered dry (pad weight ≤ 4.0 grams) at 6, 12, 18, 24, and 36 months."	Page 7 of the Synopsis
3.0	USLKR	Changed version and date.	Page 1
3.0	USLKR	Updated biostatistician information	Page 13
3.0	USLKR	Modified enrollment to a 2:1 Altis:Comparator ratio.	Page 16, Section 3.2.1
3.0	USLKR	Adjusted statistical considerations to account for a 2:1 Altis:Comparator ratio. Also clarified how missing data would be handled and defined sensitivity analyses.	Pages 26-32, Section 7
4.0	USKVE	Changed version and date.	Page 1
4.0	USKVE	The number of required study subjects is returned to 178 per group (equal allocation) as in the previous FDA approved protocol version 2.1.	Page 6 of the Synopsis and Page 16
4.0	USKVE	Updated sponsor representative information.	Pages 11, 13, 40
4.0	USKVE	The number of study subjects is returned to 178 subjects per group (equal allocation) as in the previous FDA approved protocol version 2.1.	Pages 30-31 in Section 7.9