Coloplast Corp Altis

522 Trial

Statistical Analysis Plan
Version 4.0
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Clinical Study Plan: Version 4.0 (dated November 01, 2018)

Document Approval

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1. Purpose

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analysis of data collected under the Altis 522 protocol.

2. Scope

This SAP should be read in conjunction with the study protocol and electronic case report forms (eCRF). This version of the plan has been developed with respect to the Altis 522 protocol version 4.0, dated November 01, 2018. Any changes to the protocol or eCRFs may necessitate updates to the SAP. If differences exist between the protocol and the SAP, the SAP shall prevail.

3. Applicable Documents

Document Number	Document Title
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)

4. Software

All tables, listings and figures will be produced using SAS Version 9.4 (SAS Institute, Cary, NC.) or a later version of SAS. All output will be in Microsoft Word, Microsoft Excel or RTF format. Other reporting software (such as R) may be used for data analysis, summarizations or visualization of data as necessary.

5. Trial Objectives

The purpose 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 of this study are:

1. 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.
2. 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.

The secondary objectives of this study are:

3. 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.
4. 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.
5. To provide a descriptive comparison at all time points (6, 12, 18, 24, 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.

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

6. Trial Hypotheses

7.1. Primary Effectiveness Hypotheses

The objective of the primary effectiveness analysis is 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 and is represented by the following hypotheses:

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

H_0: $\pi_C - \pi_T \geq 0.15$
H_A: $\pi_C - \pi_T < 0.15$

where π_C is the proportion of subjects in the Comparator group meeting the primary effectiveness endpoint and π_T is the proportion of subjects in the Altis group meeting the primary effectiveness endpoint and 0.15 is the non-inferiority margin.

7.2. Primary Safety Hypotheses

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 π_C is the proportion of subjects who have the primary safety endpoint during follow-up in the Comparator group and π_T is the proportion of subjects who have the primary safety endpoint during follow-up in the Altis group and 0.10 is the non-inferiority margin.

7.3. Secondary Safety Hypotheses

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 π_C is the proportion of subjects who have the secondary safety endpoint during follow-up in the Comparator group and π_T is the proportion of subjects who have the secondary safety endpoint during follow-up in the Altis group and 0.15 is the non-inferiority margin.

7.4. Revision/Resurgery Hypotheses

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 π_C is the proportion of subjects who have the revision/resurgery endpoint during follow-up in the Comparator group and π_T is the proportion of subjects who have the revision/resurgery endpoint during follow-up in the Altis group and 0.10 is the non-inferiority margin.

7. Trial Success Criteria

The Altis 522 will be evaluated according to the primary effectiveness and safety objectives. The study will be considered a success if both primary objectives (effectiveness and safety) are met.

8. Trial Design

This 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, 12, 18, 24 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 the inclusion criteria and none of the exclusion criteria will be included in the study. Subject enrollment will continue until the required sample size is successfully reached. No site may enroll more than 20% of subjects without prior approval from Coloplast Corp.

Schedule of Procedures:

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.

8.1 Randomization

This is not a randomized study.

8.2 Blinding

This is an open-label study as the study subjects and investigational study personnel are not blinded to study group assignment.

9. Sample Size Considerations

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 (two-sided; equivalent to one-sided 0.025) 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.

10.1. 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 Comparator 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.

10.2. 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. 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. This resulted in total of 284 subjects required (142 subjects per group). As all subjects are accounted for in the final analysis (subjects with missing data will be assumed to be free of such an adverse event), no accounting for attrition is necessary.

10.3. Sample Size Estimation for Powered Secondary Safety Endpoints

The total sample size required to meet the primary safety and effectiveness objectives is 262 subjects not accounting for attrition. The overall rate of device or procedure related adverse events in the IDE study is 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 per study group, for a total of 224 subjects is required to power for the assessment of the secondary safety endpoint.

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 margin as the primary safety endpoint.

10.4. Level of Significance and Power

All tests of significance will be performed at the two-sided 0.05 significance level (one-sided 0.025), unless otherwise specified. As both the primary effectiveness and safety objectives must be met for study success, no adjustment for multiplicity is required. Additionally, the powered 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.

10. Data Structure and Handling

11.1. Data Handling and Transfer

Programming of analysis datasets, tables, figures and listings will be conducted during the data management phase of the study. Tables, figures, and listings may be reviewed prior to final data lock for data review. Any data values requiring investigation or correction will be identified, and protocol deviations will be reviewed. The final run of outputs will take place after the data is deemed final.

11.2. 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 Section 12.6 below. No missing data handling procedures for the other secondary endpoints are pre-defined.

11.3. Visit Windows

All data attributed to a time point per the CRF will be included in the analysis of that time point, regardless if it is out of window.

11. Statistical Analyses

12.1. General Considerations

All analyses will be performed by an independent 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. Unless otherwise specified, two-sample t-test for independent groups or paired t-test will be used to test the means of continuous measures between groups, as appropriate. If assumptions of parametric tests are grossly violated, an equivalent non-parametric method may be sought. Fisher's exact test or binomial test will be employed to test categorical (including dichotomous) measures between groups.

The surgery date will be considered study day 0.

12.2. Analysis Populations

A subject is considered enrolled once signed informed consent is obtained. The **Intent-to-Treat (ITT)** analysis population consists of all enrolled subjects, and will be used as the supplementary population to assess the primary effectiveness endpoint results.

The **modified Intent-to-Treat (mITT)** analysis population is a subset of the ITT population, and includes all enrolled subjects who have undergone a sling implant attempt for stress urinary incontinence using either Altis SIS or an FDA cleared transobturator or retropubic sling. The mITT analysis population is the primary analysis population for the assessment of all safety and effectiveness endpoints.

The **Per-Protocol (PP)** population includes all subjects in the mITT 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 mITT analysis population. If the Per-Protocol analysis population does not differ from the mITT analysis population, separate analyses will be not presented.

12.3. Subject Disposition

Subject disposition will be presented by:

- Summary of subjects per visit
- Summary of early withdrawal and reason for early withdrawal.

12.4. Demographics and Baseline Characteristics

Demographics and baseline characteristics of the ITT analysis population will be summarized. These factors will include (but not be limited to):

- Age
- Ethnicity

- Race
- BMI
- Medical history (including diagnosis of SUI)
- Parity
- Smoking status
- Diabetes
- Hysterectomy status
- History of Multiple UTIs

In order to assess if the Altis and Comparator study populations are similar, demographics and baseline characteristics will be compared by t-tests for continuous factors and chi square tests for categorical factors, or non-parametric tests as appropriate. A propensity score analysis will also be performed. If significant differences are found between groups, the impact of relevant factor(s) on success rates will be assessed.

12.5. Study Endpoints

12.5.1. Primary Safety Endpoint

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

12.5.2. Primary Effectiveness Endpoint

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

12.5.3. 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 through 6, 12, 18, 24, and 36 months post index procedure. The rate of events through 36 months will be considered the powered endpoint.
- Observed revision/re-surgery through 6, 12, 18, 24, and 36 months post index procedure. The rate of events through 36 months will be considered the powered endpoint.
- All observed adverse events through 6, 12, 18, 24, and 36 months post index procedure

12.5.4. Secondary Effectiveness Endpoints

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

12.6. Analyses of Primary Endpoints

12.6.1. Primary Effectiveness Analyses

For the purpose of the primary effectiveness analysis, a subject will be considered a success at 6 months if there is a ≥ 50% reduction in pad weight from baseline in the mITT analysis population. A subject with < 50% reduction in pad weight from baseline will be considered a failure.

Main Analysis

The number and proportion of subjects 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 (Comparator – Altis) is less than 0.15. If non-inferiority is achieved and the upper limit of the 95% confidence interval for difference in proportions (Comparator – Altis) is less than 0, superiority of Altis can also be claimed. As this follows a simple closed test procedure, no multiplicity adjustment is necessary.

The primary analysis of this endpoint will include all available data and 'presumed failures' from the mITT 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 (1) to an adverse event, including death, or (2) to a device failure. 'Presumed failures' will be considered failures for all primary effectiveness endpoint analyses. 'Presumed failures' will contribute available data up to the point of failure, and will be considered failures in the primary effectiveness endpoint analysis after the point of failure. Subjects with missing data for other reasons will be ignored in the primary analysis. As described above, the primary effectiveness endpoint will also be summarized for the PP analysis set, following the same logic as the main analysis in the mITT analysis set.

Sensitivity Analyses

The following sensitivity analyses will be performed on the primary effectiveness endpoint:

- An analysis utilizing multiple imputation (MI) for missing values will be performed for the primary effectiveness endpoint based on the mITT analysis population. Selection of variables for the MI analysis will be performed by first assessing the correlation of relevant baseline variables including, but not limited to: baseline age, investigational site, and baseline pad weight. The initial list of candidate variables may be adjusted to allow for proper model convergence. A total of 100 imputed datasets will be created to determine the imputed effect size.
- The primary effectiveness endpoint will also be assessed in the ITT analysis population. Again, multiple imputation method will be employed to impute missing values.
    - A comparison of relevant baseline and clinical variables between missing and non-missing subjects will also be used to assess the likelihood that missingness is differential or non-differential. Non-differential missingness with respect to the outcome is known to not bias results, but to attenuate a

given effect size. Should missing subjects and non-missing subjects demonstrate high concordance on baseline factors, it can be reasonably argued that missingness is non-differential and therefore results from complete case analyses are unbiased.

- Additional sensitivity analyses for the primary effectiveness endpoint will include best case, worst case and tipping point analysis, and will be based on the mITT analysis set.

Subjects who are considered 'presumed failures' will still be considered failures in the sensitivity analyses, while outcomes for subjects with missing values for other reasons will be imputed.

12.6.2. Primary Safety Analyses

Main Analysis

The number and proportion of subjects experiencing device- and/or procedure-related serious adverse events will be tabulated for each study group. Non-inferiority through 36 months will be calculated using a normal approximation test (Z-test) for a difference in binomial proportion. Non-inferiority will be achieved if the lower limit of the 95% confidence interval for the difference in proportions (Comparator – Altis) is greater than -0.10 in the mITT analysis population. If non-inferiority is achieved and the lower limit of the 95% confidence interval for difference in proportions (Comparator – Altis) is greater than 0, superiority of Altis can also be claimed. As this follows a simple closed test procedure, no multiplicity adjustment is necessary.

The primary analysis of this endpoint will include all available data from the mITT analysis population. Subjects that have not experienced a device- and/or procedure-related serious event and who have missing data at 36 months will be assumed to be free of such an adverse event.

Sensitivity Analyses

The potential impact on the endpoint inference of all subjects with missing primary safety endpoint data 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. All sensitivity analyses will be based on the mITT analysis set.

12.6.3. Propensity Score Analysis

In addition to the analyses of the primary effectiveness and safety endpoints noted above, a propensity analysis will be conducted to address the effect of potential confounding variables on study conclusions. 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

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.

12.7. Analyses of Secondary Endpoints

The primary analyses for the secondary endpoints will be conducted using all available data in the mITT population, however, various sensitivity analyses will be presented as detailed below.

All analyses for the secondary effectiveness endpoints will be presented for the mITT and PP analysis populations, while mITT analysis population only will be used for safety endpoints. No imputation for missing data for the secondary endpoints is planned.

12.7.1. Secondary Safety Analyses

Main Analysis

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. Non-inferiority will be achieved if the lower limit of the 95% confidence interval for the difference in proportions (Comparator – Altis) is greater than -0.15 in the ITT analysis population. If non-inferiority is achieved and the lower limit of the 95% confidence interval for difference in proportions (Comparator – Altis) is greater than 0, superiority of Altis can also be claimed. As this follows a simple closed test procedure, no multiplicity adjustment is necessary.

The primary analysis of this endpoint will include all available data from the mITT analysis population. Subjects that have not experienced a device- and/or procedure-related event and who have missing data at 36 months will be assumed to be free of such an adverse event.

Sensitivity Analyses

The potential impact on the endpoint inference of all subjects with missing endpoint data 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. All sensitivity analyses will be based on the mITT analysis set.

12.7.2. Revision/Resurgery Analyses

Main Analysis

The number and proportion of subjects experiencing any revision/resurgery 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. Non-inferiority will be achieved if the lower limit of the 95% confidence interval for the difference in proportions (Comparator – Altis) is greater than -0.10 in the mITT analysis population. If non-inferiority is achieved and the lower limit of the 95% confidence interval for difference in proportions (Comparator – Altis) is greater than 0, superiority of Altis can also be claimed. As this follows a simple closed test procedure, no multiplicity adjustment is necessary.

The primary analysis of this endpoint will include all available data from the mITT 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.

Sensitivity Analyses

The potential impact on the endpoint inference of all subjects with missing endpoint data 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. All sensitivity analyses will be based on the mITT analysis set.

12.7.3. 24-Hour Pad Weight

There are both continuous and categorical measures evaluated in association with the 24-hour pad weight. Differences in 24-hour Pad Weight will be assessed at 6, 12, 18, 24, and 36 months. Summary statistics for 24-Hour pad weight and change from baseline will be summarized by group and visit. The change from baseline in 24-hour pad weight will be tested separately at each specific timepoint for superiority of the Altis group compared to the Comparator group, and will be based on the mITT analysis population. As 24-hour pad weight and change from baseline in 24-hour pad weight are not study endpoints, only available data will be included with no imputation for missing data.

Additionally, change from baseline in 24-hour pad weight in the Altis group will be compared to the Comparator group using a linear mixed model with repeated effects to understand the effect of pad weight changes over time. An unstructured correlation matrix will be specified to allow for maximal flexibility, but if convergence is not achieved, an autocorrelated or compound symmetry matrix will be used instead. An interaction term for time and treatment will also be assessed in the mixed model.

The secondary effectiveness endpoint of proportions of subjects with $\geq 50\%$ reduction in pad weight from baseline will be summarized by treatment group and visit, and will be tested for difference is proportions separately at each specific timepoint. The analysis of these endpoints will be based on the mITT analysis population, and will mimic the analysis of primary effectiveness endpoint where only available data will be included, with the exception of presumed failures.

The secondary effectiveness endpoint of proportions of subjects considered dry (pad weight ≤ 4.0 grams) will be summarized by treatment group and visit. Difference between groups in the proportion of subjects dry will be presented, and tested for difference in proportions separately at each specific timepoint. The analysis of these endpoints will be based on the mITT analysis population, and will mimic the analysis of primary effectiveness endpoint where only available data will be included, with the exception of presumed failures. Further, the proportion of subjects dry based on the 1.3 gram cutoff instead of 4.0 grams will be assessed in a similar manner.

12.7.4. Quality of Life

Change in Quality of life (QoL) scores (PGI-I, UDI-6, IIQ-7, SSQ-8) and VAS pain scores from baseline to follow-up will be summarized at each visit and for the Altis and Comparator group. Missing or incorrectly documented responses within a questionnaire will be handled according to the scoring algorithms. For each questionnaire, the Altis group will be compared to the Comparator group using a linear mixed model with repeated effects. An

unstructured correlation matrix will be specified to allow for maximal flexibility, but if convergence is not achieved, an autocorrelated or compound symmetry matrix will be used instead. An interaction term for time and treatment will also be assessed in the mixed model. Differences between the Altis group and the Comparator 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.

12.7.5. All Adverse Events

All adverse events will be summarized through 6, 12, 18, 24, 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. No imputation for missing data for the rates of adverse events is planned (with the exception of the secondary safety endpoints noted above). All safety summarized are based on mITT analysis population. Adverse events for subjects excluded from mITT analysis population (i.e., enrolled, but no implant was attempted) will be listed separately.

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. Peri-operative adverse events will be summarized by relatedness separately for each treatment group.

Clinical Events Committee (CEC) will be used to adjudicate device and procedure related serious adverse events, and other events as deemed appropriate. The CEC adjudication will be used for all safety analyses. If an adverse event has not been reviewed by the CEC, the investigator's assessment will be used for all safety analyses.

Both the CEC and the investigator will assess the device and the procedure relatedness of the adverse event. The relatedness will be categorized as "definite", "probable", "possible", "not related" or "unknown". If the event is categorized as having a "definite", "probable" or "possible" relationship, it will be considered related for all safety analyses.

12.8. Interim Analyses

No formal interim analyses for this study are planned. However, per regulatory requirement set forth by FDA, interim (or annual, as required) post-market surveillance reports will be submitted. These reports will include all the required elements (e.g., summary of subject population, study milestones/enrollment 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.

12.9. Exploratory Analyses

It is of interest to understand the time effect of treatment. Change from baseline in 24-hour pad weight as well as the proportions of subjects with ≥ 50% reduction in pad weight from baseline will be summarized by treatment group and visit. The time effect will be assessed by fitting a linear mixed model with repeated effects. An unstructured correlation matrix will be specified

to allow for maximal flexibility, but if convergence is not achieved an autocorrelated or compound symmetry matrix will be used instead. An interaction term for time and treatment will also be assessed in the mixed model.

Additional, ad hoc exploratory analyses may be conducted.

12.10. Subgroup Analyses

At a minimum, primary and secondary effectiveness endpoints will be analyzed for subjects who had baseline urinary leakage of ≥4g as assessed by the 24-hour pad weight. Similar analyses will be performed based on the baseline urinary leakage of ≥1.3 grams as assessed by the 24-hour pad weight. Other subgroup analyses may be performed as appropriate for the question of interest.

12.11. Other Data

Protocol deviations will be listed and summarized.

12. Quality of Life Measures

The following Quality of Life (QoL) measures will be collected during the study.

13.1 Patient Global Impression of Improvement (PGI-I)

The PGI-I questionnaire will be completed by the subject at 6, 12, 18, 24 and 36 months and consists of a single question about the subject's urinary condition now compared to pre-treatment. The 7-point Likert-type scale ranges from "Very much better" (1) to "Very much worse" (7).

13.2 Urogenital Distress Inventory (UDI-6)

The UDI-6 questionnaire will be completed by the subject at baseline, at 6, 12, 18, 24 and 36 months. It consists of 6 questions, with the 4-point Likert-like response scale to each question ranging from "Not at all" (0) to "Greatly" (3).

13.3 Incontinence Impact Questionnaire-Short Form (IIQ-7)

The IIQ-7 questionnaire will be completed by the subject at baseline, at 6, 12, 18, 24 and 36 months. It consists of 7 questions, with the 4-point Likert-like response scale to each question ranging from "Not at all" (0) to "Greatly" (3). IIQ-7 is intended to complement UDI-6.

13.4 Surgical Satisfaction Questionnaire (SSQ-8)

The SSQ-8 questionnaire will be completed by the subject at 6 months. It consists of 8 questions and assesses subject satisfaction following surgery to correct urinary incontinence and/or pelvic organ prolapse. It consists of total of 8 questions, with six of the 8 questions having 5-point Likert-like responses ranging from "Very satisfied" to "Very unsatisfied". The remaining two questions have a 5-point Likert-like response scale ranging from "Yes" to "Never".

13.5 Visual Analog Scale (VAS)

The VAS will be completed by the subject at baseline and at 6 months following the index procedure. In addition, 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.

13. Validation

Validation of statistical programs will be performed for any analyses sent to the FDA, provided for publication or as requested by Coloplast. Validation level required will be specified by Coloplast.

14. Version History

Version	Date	Changes
1.0	07 SEP 2017	Initial version.
2.0	01 NOV 2018	• Revised power analysis to account for equal allocation. • Clarified analysis populations. • Added subgroup analyses.
3.0	21 MAR 2021	• Updated analysis populations. • Detailed additional sensitivity analyses for the primary effectiveness endpoint, including details of imputations. • Added analysis for 1.3 gram cutoff for proportion of dry. • Elaborated on exploratory analyses.
4.0	08 AUG 2021	• Added details on analyses of secondary endpoints. • Replaced treatment group with 'Altis' and control group with 'Comparator'. • Added document approval section. • Added superiority testing if non-inferiority is achieved. • Revised section 12.7.3 (24-Hour Pad Weight) to distinguish between endpoints and associated analyses.

15. References

NA