The Safety and Efficacy of a New Adjustable Single Incision Sling for Treatment of Female Stress Urinary Incontinence Through 12-months of Follow-up

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Abstract

Purpose: The purpose of this report is to describe the safety and efficacy of the Altis® Single Incision Sling System (Altis sling) for treatment of female stress urinary incontinence through 12 months.

Materials and Methods: This study collected a variety of safety and efficacy measures relevant to assessment of urinary incontinence. The primary efficacy endpoint was improvement in 24-hour pad weight test. Other efficacy measures included Cough Stress Test, Urogenital Distress Inventory-Short Form, Incontinence Impact Questionnaire-Short Form, Patient Global Impression of Improvement, and 3-day voiding diary. Safety was evaluated through assessment of device and procedure-related adverse events.

Results: Of 116 surgical attempts, 113 subjects were implanted with the Altis sling. 103 had primary efficacy data at baseline and 6 months, and 101 had efficacy data at baseline and 12 months. Consequently, 88 (85.4%) subjects at 6 months and 91 (90.1%) at 12 months achieved ≥50% reduction in pad weight. The Cough Stress Test was negative for 95 (92.2%) subjects at 6 months and 91 (90.1%) at 12 months. A decrease in median leaks per day was observed at 6 months and improvements in all **patient reported** measures were **observed** through 12 months. A majority of subjects reported feeling "much better" or "very much better" at 6 and 12 months. There were no reports of mesh erosion or migration, and no unanticipated adverse events through 12 months.

Conclusions: The Altis sling appears to be safe, efficacious, and performs as intended in the treatment of stress urinary incontinence through 12 months.

Introduction

Urinary incontinence affects up to 50% of women[1,2] and of these, 50 to 80% are identified as having stress urinary incontinence (SUI).[3,4] An estimated 4 to 10% of women in the United States (U.S.) undergo surgery to restore continence and this rate has increased steadily during the past 20 years.[5]

Traditional surgical techniques such as Burch colposuspension and autologous sling procedures achieve positive results but require general anesthesia and hospitalization. In 1996, the Tension-free Vaginal Technique (TVT®) transformed the way female SUI was treated. Petros and Ulmsten presented an integral theory of the physiopathology of stress urinary incontinence[6] and introduced a modified intravaginal slingplasty procedure to treat SUI. The procedure was less invasive and feasible under local anesthesia and eventually was a suitable in-office procedure.[7] The cure rate was durable years after the operation, but retropubic tension free sling procedures were associated with increased morbidity such as bladder perforation, pain, voiding dysfunctions, de novo urge incontinence, as well as rare serious complications such as vascular, nerve or bowel injury and death.[8,9]

The transobturator approach was developed in 2001 to minimize the morbidity associated with blind passage of the needle in the retropubic space.[10] Randomized clinical studies comparing retropubic and transobturator tension-free procedures have shown that both procedures have similar efficacy.[11]

Abdel-Fattah, et al., recently proposed classification of midurethral slings into three generations. The first generation is represented by tension-free retropubic slings, the second generation are devices utilizing the transobturator route (outside-in and inside-out), and the third

generation represented by single incision slings.[12] Single incision slings vary in size, surgical technique, and fixation technology, with the common feature of a single vaginal incision.

The aim of this study was to assess the safety and efficacy of the Altis® Single Incision Sling System in the treatment of female SUI. The Altis sling (Coloplast Corp, Minneapolis Minnesota, U.S.) is an adjustable, low elasticity, minimally invasive single incision sling. The device was cleared to market in the U.S. in November 2012.

Materials and Methods

This prospective, single arm, multi-center study included 17 sites in the U.S. and Canada. All sites received Institutional Review Board approval and all subjects provided written informed consent prior to enrollment.

Inclusion criteria included women at least age 18, with SUI confirmed through Cough Stress Test (CST) or urodynamic evaluation, and who had failed two non-invasive incontinence therapies (e.g. Kegel exercise, behavior modification, biofeedback, etc.). Subjects were excluded if they had neurogenic or urge predominant incontinence, active urogenital infection, pelvic organ prolapse ≥Stage II, atonic bladder or post-void residual volume consistently greater than 100 milliliters, prior surgical treatment for incontinence, or if they were pregnant or planning to become pregnant.

At baseline, a physical exam was performed and the subject's medical history was documented. A 24-hour Pad Weight Test (PWT) was completed. A standardized CST was performed with subjects in the lithotomy and standing positions after filling the bladder to functional capacity with normal saline. Subjects were asked to cough 5 times in each position and any leakage was considered a positive test. Post-void residual volumes were determined by bladder scan, ultrasound, or catheter. **The presence of urge predominant incontinence was**

assessed through clinical evaluation, medical history and prior non-study testing as available. Validated questionnaires consisting of Urogenital Distress Inventory-Short Form (UDI-6) and Incontinence Impact Questionnaire-Short Form (IIQ-7) were obtained.

The Altis sling (Figure 1) is a 7.75cm polypropylene mesh attached to suture extending to one static and one dynamic anchor. The dynamic anchor allows intra-operative adjustability and tensioning to achieve continence. A set of helical-type disposable introducers are used to position the anchors.

Surgery was performed in hospitals, ambulatory care centers, or in-office, under general, spinal, or local anesthesia. No concomitant pelvic floor surgical procedures were allowed. The Altis sling was implanted according to the product's Instructions for Use. All surgeons had prior experience implanting other sling systems and received product-specific surgical training. The surgical procedure consisted of a mid-urethral incision on the anterior vaginal wall with bilateral dissection to the obturator internus fascia at the point of the medial border of the inferior ramus. Using the introducer, the static anchor was placed through the obturator membrane with an inside-out approach. The dynamic anchor was then placed on the contralateral side ensuring that the sling was lying tension free and flat under the mid-urethra. The bladder was filled with saline and depending on the subject's level of anesthesia the subject was instructed to cough or a Credé maneuver was performed while the sling was tensioned to the desired level of continence.

In-clinic **standardized** follow-up visits occurred at 3, 6, and 12 months with **physical examination and urodynamic studies, including** 24-hour PWT, CST, **inspection of vaginal incision**, UDI-6, IIQ-7, and Patient Global Impression of Improvement (PGI-I) collected at each visit. Additionally, a 3-day voiding diary was collected at baseline and 6 months. Safety was

evaluated through assessment of device and procedure related adverse events throughout the study.

The primary efficacy endpoint was improvement in the 24-hour PWT at 6 months. Clinically meaningful improvement was defined as ≥50% reduction in pad weight from baseline following the recommendation within the U.S. Food and Drug Administration guidance document on the treatment of urinary incontinence.[13] **We also established a performance goal that we defined as at least 50% of patients meeting the clinically meaningful** improvement criterion. **We evaluated the percentage of subjects with a clinically meaningful improvement using a one-sided binomial test comparing the observed rate against the (null) of 50%.**

The primary endpoint was also tested at the 12 month time point. A Wilcoxon sign-rank test was used to test for a significant change from baseline in the continuous parameter of pad weight. Summary statistics were calculated for all meaningful study variables. Means, standard deviations and ranges were calculated for continuous variables. The analysis cohorts for the secondary endpoints included all subjects with available endpoint data. All statistical analyses were conducted with SASv9.3.

Results

The mean age of implanted subjects was 54.5±14.0 years with an average body mass index of 31.2 ±6.8. At enrollment, all subjects had confirmed SUI through CST or urodynamic testing. At baseline, 71 (62.8%) implanted subjects presented with SUI-alone and 42 (37.2%) presented with mixed incontinence. Seventy-nine subjects (69.9%) had previously practiced behavioral modification and 56 (49.6%) had used physical therapy including Kegel exercise.

A total of 116 subjects underwent a procedure attempt between December 2010 and January 2012 and 113 were successfully implanted. Three procedures were aborted intraoperatively due to technical observation (bent introducer tip due to surgical technique), intraoperative exclusion (eroded prolapse mesh was discovered during surgery and required treatment), and anatomic variation (subject's pelvis was too wide). The mean duration of the implant procedure was 12.7±8.0 minutes with nearly half performed using spinal or local anesthesia (Table **1**).

Four implanted subjects (3.5%) withdrew consent prior to the 6 month visit and an additional four subjects (3.5%) withdrew consent prior to the 12 month visit (Figure 2). Subjects who withdrew consent indicated changes in family, work, or health care provider status; however, one subject withdrew consent following unsuccessful revision surgery for mesh extrusion. Median follow-up on subjects withdrawn prior to 12 months was 7.3 months.

Of implanted subjects, 103 had primary efficacy data at baseline and 6 months; 88 (85.4%) of these subjects achieved ≥50% improvement in pad weight ($P<0.0001$) (Table **2**). Therefore, the criterion for clinically meaningful improvement was met. Sensitivity analyses were performed to assess data robustness. Using the last value carried forward, 3 month data was imputed for missing 6 month data, finding 97 (86.6%) subjects with improvement and a lower confidence bound of 79.8% ($p<0.0001$). Subsequently, using a worst case scenario by imputing failure for all implanted subjects with no 6 month data finds 88 (77.9%) of subjects with improvement at a lower confidence bound of 70.1% ($p<0.0001$). In addition, poolability was assessed across study sites which included high and low enrolling sites using the Pearson's chi-squared test. In this assessment, a p-value difference of 0.22 was found in pad weight improvement at 6 months; therefore, we consider the data to be poolable across study sites.

At 12 months, 101 subjects had pad weight data at both baseline and 12 months. Median pad weight decreased 18.1g (IQR: 7.2, 49.8) from baseline and 91 (90.1%) subjects achieved ≥50% reduction in pad weight at12 months ($p<0.0001$). CST was negative for 95 (92.2%) subjects at 6 months and 91 (90.1%) at 12 months (Table **3**). Results of the 3-day voiding diary found a decrease in median leaks from 3.7 at baseline to 0 at 6 months. Per PGI-I results, 92 (87.6%) subjects at 6 months, and 92 (89.3%) at 12 months, reported feeling "much better" or "very much better". Improvements in **patient reported measures** were observed with median decreases from baseline in UDI-6 scores of 44.4 (IQR: 33.3, 55.5) at both 6 and 12 months. In addition, median decreases from baseline in IIQ-7 scores of 47.0 (IQR: 24.0, 66.0) were observed at both 6 and 12 months.

There were no reports of mesh erosion, migration, or foreign body reaction through 12 months (Table **4**). There were three serious adverse events (SAEs). One SAE included a pelvic hematoma that developed following revision surgery due to urinary outlet obstruction. The second event involved a mesh extrusion that was conservatively categorized as an SAE due to subject withdrawal prior to the completion of revision surgery where device explant was indicated. The third event was a mesh extrusion where the sling was trimmed on two separate occasions.

The most common device and/or procedure-related adverse event was non-pelvic pain occurring in 9 (8%) subjects. Non-pelvic pain consisted of groin, hip, or thigh pain reported from two sites. In all cases, non-pelvic pain was defined as procedure-related with one site attributing a majority of the events to the lithotomy position required during the implant procedure. Mesh extrusion was reported in 4 (3.5%) subjects. **The median time to extrusion was 176 days from implant.** Three subjects with mesh extrusion underwent revision surgery

which included trimming and excision. **Following revision surgery, extrusion was considered resolved in two subjects while the third subject withdrew from the study prior to the determination of resolution. The** fourth subject with mesh extrusion was asymptomatic and was successfully treated with estrogen cream and therefore was not surgically treated. Two (1.8%) subjects experienced device and/or procedure-related urinary retention immediately post-procedure. These events were treated with a Foley catheter and resolved within 3 and 8 days. One (0.9%) subject experienced symptoms of urinary outlet obstruction 6 days post-procedure. This subject underwent 2 revision surgeries and ultimately the mesh was incised on both sides of the urethra and the condition resolved. In total, 6 revision procedures were performed in 4 subjects.

Discussion

Incontinence in women is a medical condition with a considerable health impact. Single incision slings represent the latest generation of medical devices designed to treat SUI. The aim of single incision slings is to reduce surgical morbidity through a single vaginal incision. Commercially available single incision slings vary in length, elasticity, type of introducer, method of fixation, and post-insertion adjustability. The Altis sling does not require a locking mechanism once fixation is achieved by anchor insertion through the obturator membrane. When compared in animal studies to four commercially available anchor-based slings, the anchors for the Altis sling were demonstrated to be robust with the least insertion force and the greatest retention pull-out force.[14] The Altis sling has bi-directional adjustability which allows for the sling tension to be controlled intraoperatively to achieve the desired level of continence.

The aim of this study was to assess the safety and efficacy of the Altis sling. We defined clinically meaningful improvement as ≥50% reduction in pad weight from baseline and we

demonstrated improvement **in 85.4% of subjects** at 6 months **and 90.1% at 12 months using this definition. Furthermore, we found that improvement was statistically significant** at both 6 and 12 months ($p<0.0001$, $p<0.0001$); **In addition**, we found that improvement remained significant when accounting for missing data using the last value carried forward and a worst case scenario. Moreover, our results show evidence of efficacy through 12 months in pad weight, CST, **and patient reported measures of UDI-6, IIQ-7, and PGI-I**. Based on recent recommendations,[15] a pad weight of ≤4 grams indicates a dry result. Using this recommendation we find 70.9% (73/103) of subjects at 6 months and 77.2% (78/101) subjects at 12 months were dry, having achieved a pad weight of ≤4 grams over a 24-hour period.

Of note, for the ten subjects with a positive CST at 12-months these subjects subjectively reported per PGI-I, "Very Much Better" (n=2), "Much Better" (n=5), "A Little Better" (n=2) and "A Little Worse" (n=1) at 12 months. Therefore, subjective results indicate that some patients are satisfied with treatment even in the absence of a complete cure. There were no reports of mesh erosion, migration, or foreign body reaction through 12 months.

This study collected a broad set of objective and subjective study endpoints that are relevant to the evaluation of urinary incontinence. We feel that the sum of collected endpoints sufficiently characterizes treatment with the Altis sling. A strength of this study includes the addition of a clinically meaningful performance criterion defined as ≥50% reduction in pad weight from baseline. While the criterion may require further study and confirmation within the medical community, we see strong improvements in **patient reported measures**, indicating that patients are satisfied with treatment following reductions in urine leakage. Other strengths of this study include the utilization of a multi-center trial design representing a real world diversity of surgical experience. Additionally, none of the U.S. sites had experience with the Altis sling in

patients prior to study initiation and yet the results found no serious intraoperative complications and reasonable success.

Limitations of this study include lack of a control group and randomization. This study takes place in surgically naïve patients; therefore, we report no data for subjects with previous surgical incontinence treatment. Additionally, a number of questions are beyond the scope of this report including evaluation of a learning curve effect and evaluation of results by baseline patient characteristics. In any case, given the small number of reported failures, it is unlikely that a statistically significant association of success according to patient or procedural characteristics would be found. In this regard, future studies with larger samples are required to fully define predictive factors that may be associated with treatment success.

Conclusion

The Altis sling is a newly available treatment option available to the medical community and this report represents the first publication of multi-center data on this product. The device offers a less invasive surgical approach with the advantage of intra-operative adjustability to achieve individualized results. Our data support the conclusion that the Altis sling appears safe, efficacious, and performs as intended through 12 months.

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Key of Definitions for Abbreviations

CST = Cough Stress Test
IIQ-7 = Incontinence Impact Questionnaire – Short Form
PGI-I = Patient Global Impression of Improvement
PWT = Pad Weight Test
SUI = Stress Urinary Incontinence
UDI-6 = Urogenital Distress Inventory – Short Form
US = United States

Table

Table 1: Procedural Characteristics of Implanted Subjects (n=113)	
Procedure location (n)	
In-patient hospital	59.3% (67)
Ambulatory care center	23.9% (27)
In-office	16.8% (19)
Anesthesia (n)	
General	52.2% (59)
Spinal	2.7% (3)
Local	45.1% (51)
Procedure duration (minutes)	
Mean±SD Median (Range)	12.7±8.0 12.0 (4.0, 56.0)

Table

Table 2: 24-Hour Pad Weight Test: Improvement at 6 and 12 months				
Time	**Success % (n/N)**	**Performance Goal**	**Lower CL**	**p-value**
6-Month	85.4% (88/103)	≥50% reduction in pad weight	**Lower 95.81% CL*** 78.1%	<0.0001
12-Month	90.1% (91/101)	≥50% reduction in pad weight	**Lower 95% CL** 83.8%	<0.0001
*The final significance level is 0.04191 accounting for one interim analysis.				

Table

Table 3: Efficacy and Patient Reported Measures Results at Baseline, 6 Months and 12 Months			
Endpoint	**Baseline**	**6 Months**	**12 Months**
24-Hour Pad Weight			
Median (IQR)	21.9 g (9.4, 57.0)	1.9 g (0.2, 5.2)	1.1 g (0.3, 4.0)
Median Reduction (IQR)		18.4 g (7.0, 46.0)	18.1 g (7.2, 49.8)
Dry ≤4.0 grams (n/N)		70.9% (73/103)	77.2% (78/101)
Cough Stress Test % Negative (n/N)	0.0% (0/112)	92.2% (95/103)	90.1% (91/101)
3-Day Voiding Diary Median leaks per day	3.7	0.0	NA
Median UDI-6 Score (IQR)	55.5 (38.9, 66.6)	5.6 (0.0, 16.7)	5.6 (0.0, 16.7)
Median Reduction (IQR)		44.4 (33.3, 55.5)	44.4 (33.3, 55.5)
Median IIQ-7 Score (IQR)	57.0 (33.0, 71.0)	0.0 (0.0, 6.5)	0.0 (0.0, 9.0)
Median Reduction (IQR)		47.0 (24.0, 66.0)	47.0 (24.0, 66.0)
PGI-I Responses % (n)			
Very much better	NA	58.10% (61)	58.25 % (60)
Much better	NA	29.52% (31)	31.07 % (32)
A little better	NA	11.43% (12)	7.77 % (8)
No change	NA	0.0% (0)	0.97 % (1)
A little worse	NA	0.0% (0)	1.94 % (2)
Much worse	NA	0.0% (0)	0.00 % (0)
Very much worse	NA	0.95% (1)	0.00 % (0)

Table

Table 4: Device and/or Procedure Related Adverse Events in Implanted Subjects (n=113)	
Adverse Event	**Number of Subjects (%)**
Other: non-pelvic pain	9 (8.0%)
Mesh Extrusion[1]	4 (3.5%)
Pelvic/urogenital pain	4 (3.5%)
Urinary retention	2 (1.8%)
Urinary tract infection	1 (0.9%)
De novo urgency	1 (0.9%)
Dyspareunia	1 (0.9%)
Inflammation	1 (0.9%)
Delayed wound healing	1 (0.9%)
Other: worsening overactive bladder	1 (0.9%)
Other: bleeding[2]	1 (0.9%)
Other: decreased urine stream	1 (0.9%)
Other: voiding dysfunction[3]	1 (0.9%)
Other: miscellaneous[4]	2 (1.8%)

[1] Includes 2 mesh extrusions categorized as SAEs
[2] Pelvic hematoma categorized as an SAE
[3] Defined as urinary outlet obstruction
[4] Includes one event of nausea and one event of a reaction to antibiotic therapy

Figure 1
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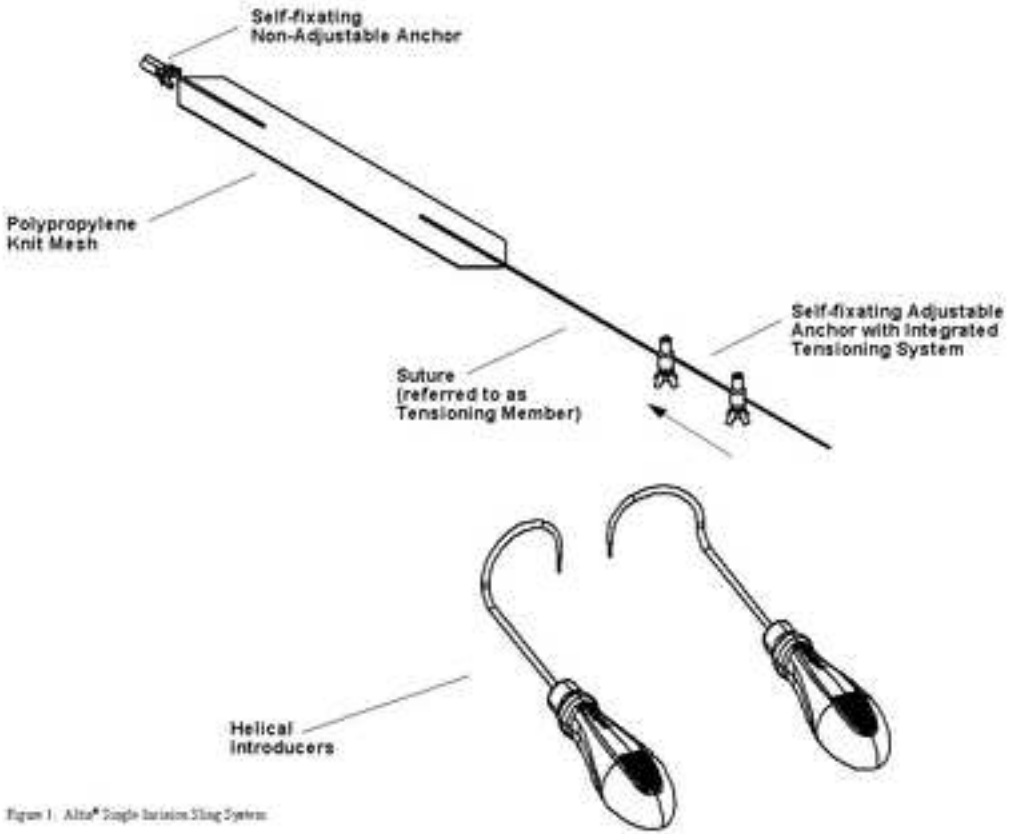

Figure 2
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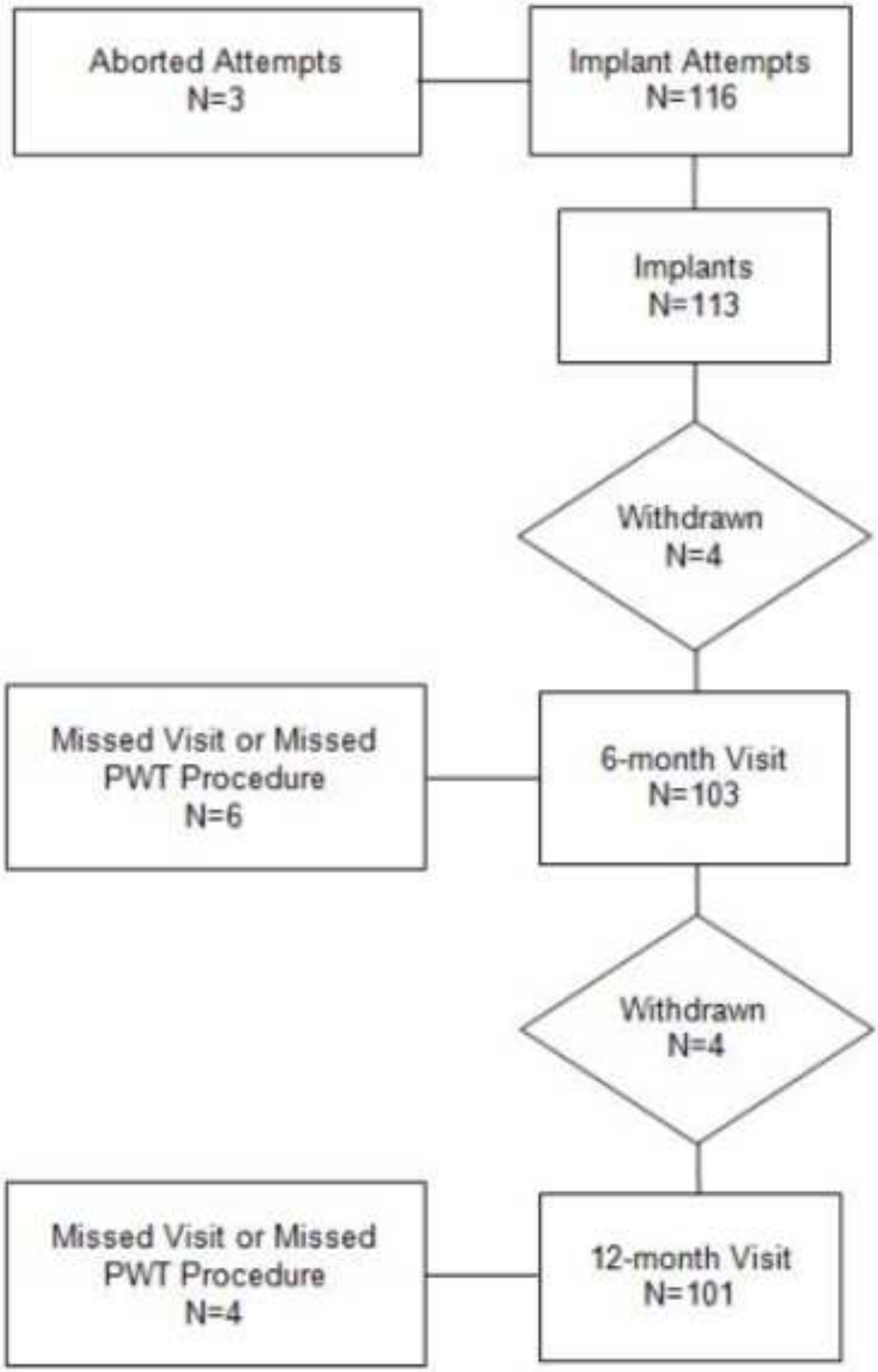

Figure 2: CONSORT Diagram for Primary Efficacy Endpoint (24-hour PWT)