SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Injectable Urethral Bulking Agent
Device Trade Name:	Macroplastique® Implants
Applicant's Name and Address:	Uroplasty, Inc. 2718 Summer Street NE Minneapolis, Minnesota 55413
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P040050
Date of Notice of Approval to Applicant:	October 30, 2006

II. INDICATIONS FOR USE

Macroplastique® Implants (hereinafter called Macroplastique) is indicated for transurethral injection in the treatment of adult women diagnosed with stress urinary incontinence (SUI) primarily due to intrinsic sphincter deficiency (ISD).

III. CONTRAINDICATIONS

Macroplastique is contraindicated in patients with the following conditions:

- acute urogenital tract inflammation or infection, or
- fragile urethral mucosal lining (e.g., post-radiation therapy, post-surgery to the bladder neck).

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Macroplastique labeling.

V. DEVICE DESCRIPTION

Macroplastique is a permanently implanted, non-pyrogenic, injectable bulking agent composed of polydimethylsiloxane (silicone elastomer) particles suspended in a polyvinylpyrrolidone (PVP) carrier gel. Macroplastique is supplied sterile in a pre-filled, 3 cc syringe, containing approximately 2.5 mL of product. Sterilization is by gamma irradiation. Injection of Macroplastique is accomplished using the Uroplasty Administration Device (a manual device used to facilitate depressing the syringe plunger) and the Uroplasty Rigid Endoscopic Needle (both sold separately).

Macroplastique is injected under cystoscopic visualization into the urethral submucosa 1.5 to 2 cm distal to the bladder neck until urethral coaptation is achieved. Following injection into the tissue, the PVP carrier gel dissipates, leaving behind the silicone elastomer particles. The injection of Macroplastique creates increased tissue bulk, resulting in reduced urinary incontinence.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Conventional procedures used in the treatment of female stress urinary incontinence include

- behavioral techniques, such as bladder training and prompted voiding;
- pelvic floor strengthening exercises (i.e., Kegel exercises), with or without device assistance, such as biofeedback, vaginal cones, and electrical stimulation of the pelvic floor muscles;
- external devices, such as absorbent products (pads/diapers), collecting devices, or occluding devices;
- internal urethral occlusion devices;
- pharmacological treatments, such as alpha-adrenergic agonists and estrogen supplements;
- other injectable bulking agents; and
- surgical treatments/procedures, such as suspension or sling procedures, and urinary diversion procedures.

VII. MARKETING HISTORY

Macroplastique is currently marketed in the European Community, Canada, Australia, and Latin America. Macroplastique has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Information on adverse events is based on 122 subjects implanted with Macroplastique in a multicenter, randomized prospective study. All study patients were adult women diagnosed as having SUI due to ISD. A total of 447 adverse events were reported during the clinical trial, of which 303 were categorized as being related to either the device or treatment (referred to as "treatment-related"). Ninety-six (96) of the 122 patients receiving treatment (78.7%) experienced at least one treatment-related adverse event.

The treatment-related adverse events that occurred during the trial at incidences of $\geq 2\%$ are summarized in Table 1. All genitourinary adverse events were classified as "treatment-related."

Table 1. Number (%) Subjects Reporting Treatment-Related Adverse Events

Event Category	**Macroplastique** (n=122)
Post-procedure catheterization	53 (43.4%)
Urinary tract infection (UTI)	31 (25.4%)
Urinary retention	26 (21.3%)
Dysuria	23 (18.9%)
Hematuria (including transient hematuria)	19 (15.6%)
Pain at implantation site	16 (13.1%)
Frequency	14 (11.5%)
Urgency	14 (11.5%)
Slowed urine stream	9 (7.4%)
Incomplete bladder emptying	7 (5.7%)
Urge incontinence	7 (5.7%)
Hesitancy	6 (4.9%)
Vaginal bleeding	4 (3.3%)
Yeast infection	4 (3.3%)
Bladder pain	3 (2.5%)
Cystitis	3 (2.5%)
Increased/worsening nocturia	3 (2.5%)
Overactive bladder (OAB)	3 (2.5%)

Most treatment-related adverse events occurred in the first 30 days following treatment. At the time of database closure, all but 30 treatment-related adverse events were documented to have resolved. The following events were persistent or had unknown resolution status at the time of database closure (listed alphabetically with the number of events shown in parentheses): abdominal pain (n=1), bladder infection (n=1), bladder infection symptoms (n=1), change in urine stream (n=2), dysuria (n=2), filling defect (n=1), frequency (n=1), hesitancy (n=2), incomplete bladder emptying (n=2), overactive bladder (n=1), pelvic tenderness (n=1), spotting between periods (n=1), sleep disturbance (n=1), slowed urine stream (n=2), tenderness at implant site (n=1) transient hematuria (n=2), urethral erosion (n=1), urgency (n=3), urge incontinence (n=3), and vaginal discharge (n=1).

One Macroplastique subject died during the study. This death was attributed to complications of breast cancer, and was deemed unrelated to the device or the implantation procedure. There were no serious unanticipated adverse device effects reported in the Macroplastique arm.

The categories of adverse events observed in this study are generally consistent with those reported in the literature for urethral bulking agents. Although not reported in the clinical study, other potential adverse events which may occur include erythema, embolic phenomena, granuloma, migration, and vascular occlusion.

Please refer to the "Summary of Clinical Studies" section for additional information on adverse events observed in the clinical study.

IX. SUMMARY OF PRECLINICAL STUDIES

Laboratory Studies

The objectives of the laboratory studies were to characterize the chemistry and physical properties of Macroplastique (final, sterilized samples) and its constituent materials (silicone elastomer particles, PVP carrier gel). The specific laboratory studies that were performed are as follows:

- silicone elastomer particle geometry and size distribution,
- gravimetric extract analysis,
- Fourier transform infrared spectroscopy analysis,
- heavy metal / elemental analyses,
- scanning electron microscopy and energy dispersive spectrometry,
- analysis of xylene residuals,
- molecular weight distribution of siloxane oligomers by gel permeation chromatography,
- analysis of D3-D6 cyclic siloxanes by gas chromatography and mass spectroscopy,
- silicone cross link density and swell ratio,
- differential scanning calorimetry,
- thermogravimetric analysis,
- PVP molecular weight analysis, and
- expressability (i.e., injection force).

The chemical analyses confirmed the identity and purity of Macroplastique and its chemical constituents. The physical tests verified the size distribution and content of silicone particles in Macroplastique, and that Macroplastique can be easily injected using the administration device. These chemical analyses and physical tests verified that the product conforms to design specifications, and demonstrated product consistency between lots.

Sterilization and Shelf Life Testing

Gamma radiation sterilization of Macroplastique-filled 3 cc syringes was validated to provide a sterility assurance level of at least 10^{-6}. Testing performed on the finished product verified that endotoxin levels were consistently maintained. The heat-sealing of the foil pouches was validated to produce consistent seals with peel strengths of 0.17-0.85 N/mm. Real-time testing on final, packaged product confirmed sterility, package integrity, and functionality for a shelf life of 2 years. These studies included simulation of shipping and handling conditions.

Acute Biocompatibility Studies

Evaluation of biocompatibility was conducted per the FDA guidance documents "Use of International Standard ISO 10993-1, 'Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing'"[1] (following the recommendations for a permanent implant). Testing was carried out in compliance with 21 CFR Part 58, "Good Laboratory Practice for Nonclinical Laboratory Studies." The following specific biocompatibility tests were performed on final, sterilized samples of Macroplastique and the syringe in which the device is packaged:

Macroplastique:

- elution cytotoxicity (MEM extract),
- delayed contact sensitization (guinea pig),
- intracutaneous irritation (rabbit),
- acute systemic toxicity (mouse),
- 7-day intramuscular implantation with histopathology (rabbit),
- material-mediated pyrogenicity, and
- genotoxicity tests (Ames reverse mutation, mouse lymphoma, and mouse bone marrow micronucleus assay).

Syringe:

- acute systemic toxicity,
- intracutaneous toxicity, and
- muscle implantation.

Syringe stopper:

- cytotoxicity,
- hemolysis,
- intracutaneous and systemic toxicity,
- physicochemistry,
- implantation,
- skin sensitization,
- mutagenicity, and
- pyrogenicity.

For each of these tests, no adverse effects or toxicity were observed and all test requirements were met.

Animal Study

A 12-month implant study was conducted to evaluate the long-term effects of Macroplastique implantation in the urethral submucosa of pigs. The objective of the study was to determine the long-term safety of injected Macroplastique by evaluating the tissue reaction locally at the implantation site, the potential for migration of Macroplastique particles from the implantation site, and the effects of Macroplastique implantation on major visceral organs remote from the implantation site.

A total of 18 female Sinclair miniature swine each received three injections of Macroplastique into the urethral submucosa (1-2 mL per injection site). All Macroplastique injections simulated the clinical use conditions of Macroplastique with regard to cystoscopic delivery, implant site, and volume of material injected. Prior to sacrifice, blood and urine samples were collected from each animal for routine hematology, clinical chemistry, and urinalysis.

Animals were sacrificed at 1 week, and 1, 3, 6, 9, and 12 months post-implantation. Each animal was necropsied, and injection sites and other tissues were inspected grossly. All implant sites were processed for histologic examination, as well as the following remote organs/tissues: brain, kidney, liver, lung, heart, spleen, inguinal lymph nodes, and urinary bladder. All of the pigs tolerated the procedure well and remained in good health during the course of the study except for one that was found dead on day 281. Following

a complete necropsy, no abnormal findings were observed. Although the cause of death was not determined, it was not believed to be related to Macroplastique implantation.

The main conclusions from the animal study are as follows:

- There was no clinical evidence that the injection procedure or Macroplastique caused untoward effects in the pigs.
- The hematology, clinical chemistry, and urinalysis findings were acceptable throughout the study.
- All findings noted during necropsy were within normal limits.
- The histological assessment of the injection sites demonstrated the formation of a well-defined capsule within 1 week, and the evolution of the tissue response from acute inflammation (at 1 month) to a stable foreign body response with mature fibrous connective tissue (3-12 months). These findings were considered to be consistent with an expected progress of reaction and subsequent healing at an implantation site.
- Histological examination of the major organs and distant sites revealed neither signs of systemic toxicity nor evidence of particle migration.

Based on the results of the acute biocompatibility studies and the animal study, Macroplastique is safe for injection into the urethral submucosa.

X. SUMMARY OF CLINICAL STUDIES

Objectives

A clinical study was conducted under IDE G990150. The objectives of the clinical trial were to assess the safety and effectiveness of Macroplastique in the treatment of female SUI due to ISD, and to demonstrate non-inferiority to a currently marketed absorbable bulking agent ("control").

Study Design

Overview

The study was a multicenter, single-blinded, randomized, controlled trial conducted at 12 institutions (10 U.S. and 2 Canada). Female patients with SUI due to ISD were randomized (1:1) to either Macroplastique or control. Following treatment, patients in both arms were assessed at regular intervals over a 12-month period. Additionally, the majority of Macroplastique patients were followed to 24 months to assess long-term safety and effectiveness. The U.S. and Canadian sites followed the same protocol.

Patient Selection

The clinical trial population consisted of women who were diagnosed with SUI due to ISD. The inclusion criteria for study enrollment were:

- Female, age ≥ 18 years with life expectancy ≥ 2 years
- Failed ≥ 6 months conservative treatment for SUI
- Urodynamics assessment demonstrates SUI primarily due to ISD
- Normal bladder capacity (> 250 mL)

- Normal bladder compliance and stability, with a maximum detrusor pressure of < 25 cm H_2O during filling cystometry
- Valsalva leak point pressure (VLPP) ≤ 90 cm H_2O
- Viable mucosal lining at the injection site
- May have concurrent mild prolapse not significantly contributing to her urinary incontinence
- Willing and able to give informed consent

The exclusion criteria included:

- Prior urethral bulking agent injection or previous implantation with an artificial urinary sphincter
- < 1 g urine leakage on the pad weight test
- Detrusor hyperreflexia
- Acute, infectious genital or urinary tract conditions
- History of gross hematuria, or has had ≥ 4 urinary tract infections (UTIs) in the past 6 months
- History of indwelling intraurethral device use, or incontinence due to an anatomical defect (congenital or traumatic)
- Morbid obesity (> 100 lbs over ideal body weight)
- Significant coexisting disease/condition or treatment regimen that may confound the study data
- Serious connective tissue disease, or is receiving immunosuppressive therapy
- Any condition that could lead to significant post-operative complications, including current infection, uncontrolled diabetes, or elevated residual urine from bladder outlet obstruction
- Pregnant, lactating, within 12 months post-partum, or planning to become pregnant in next 24 months
- Positive reaction to the skin test for the control bulking agent

Hypothesis/Sample Size

The primary success criterion for sample size determination was improvement of at least one incontinence grade (i.e., Stamey Grade) at 12-month follow-up, compared to baseline grade. The study hypothesis was that the proportion of Macroplastique subjects meeting the primary success criterion is no worse than that observed in the control arm minus some maximum allowable difference (δ). A minimum required sample size of 208 patients was calculated (104 per arm), based on an equivalence trial using the Blackwelder formula and the following assumptions:

α (one-sided type I error) = 0.05
β (type II error) = 0.20
δ (difference between the effectiveness of the test and control devices) = 0.15
P1 = P2 = 0.75 (expected success based on the primary endpoint)

The protocol specifies that the primary comparisons of Macroplastique effectiveness will be assessed using the intent-to-treat approach, where all subjects without data at 12 months will be imputed as failures.

Primary Effectiveness Endpoint

Stamey Grade

The primary success criterion for the study was improvement (decrease) of ≥ 1 incontinence grade from baseline to 12 months post-treatment. The incontinence grading scale used as the primary effectiveness endpoint for this study was defined by Stamey in 1979[2], and has been used in various incontinence studies. Using information from a 3-day patient diary and physical examination, the physician graded the severity of incontinence using the following scale:

Grade 0: Continent (dry).
Grade 1: Urine leakage associated with stressful activities, i.e., lifting weights, coughing, or sneezing, but never in bed at night.
Grade 2: Urine leakage associated with activities of minimal stress, i.e., walking or standing up.
Grade 3: Urine leakage occurs at all times, with any activity, irrespective of position.

In addition to Stamey Grade improvement at 12 months, the study also assessed (i) the Stamey Grade improvement at follow-up intervals other than 12 months, and (ii) the number of patients who were dry on Stamey Grade at each follow-up interval.

Secondary Effectiveness Endpoints

Pad Weight Test

The amount of urine loss was quantified through the use of absorbent pads, which were worn by patients and then weighed after 1 hour following the completion of certain prescribed activities (i.e., walking, stair climbing, sitting/standing, coughing, running, and bending down). Prior to testing, patients were required to drink 500 mL of fluid within 15 minutes. Pad weight effectiveness was defined as a decrease in pad weight of ≥ 50% at 12 months, compared to baseline. In addition, mean urine leakage (in grams) during pad weight testing was compared before and after treatment.

Incontinence Quality of Life (IQOL) Questionnaire

The IQOL questionnaire is a validated instrument consisting of 22 questions[3]. The patient assigns a score of 1 to 5 to each question (maximum score = 110), with higher scores indicating better quality of life. Mean IQOL scores were reported for each follow-up interval and assessed for changes.

Subject Self-Assessment/Physician Assessment

At 12 months, subjects were asked to subjectively assess the degree of improvement (i.e., cured/dry, marked improvement, slight improvement, unchanged), as well as to estimate their pad usage (i.e., more, same, or less than baseline). Similarly, physicians were asked to assess the degree of improvement in each patient at 12 months (i.e., cured/dry, marked improvement, slight improvement, or unchanged).

Safety Endpoint

Safety was evaluated by comparing the incidence and severity of complications and adverse events for the Macroplastique and control treatment arms.

Patient Assessments

Screening

Patients willing to participate in the study and who gave informed consent underwent an evaluation for their urinary incontinence. This evaluation included a medical and incontinence history, physical examination, urodynamics (VLPP, cystometrogram, uroflowmetry), pad weight test, 3-day incontinence diary, and IQOL questionnaire. Additionally, patients received urinalysis, blood work, the skin sensitivity test for the control bulking agent, and a pregnancy test (if applicable). Only those individuals satisfying the inclusion and exclusion criteria were randomized. An initial cystoscopic examination was performed on the day of treatment, immediately prior to the bulking procedure.

Treatment

Eligible patients were randomized to treatment with either Macroplastique or the control bulking agent. Treatment consisted of injections of urethral bulking agent at one or more sites within the urethra (typically three), and was performed as an outpatient procedure. Patients were blinded to the treatment they received (Macroplastique or control).

Macroplastique and the control bulking agent were delivered to the urethral submucosa via a transurethral route of injection under cystoscopic visualization. Control treatments were performed according to the approved instructions for use. Macroplastique injections were administered as follows: (i) prime the endoscopic needle with EZ-Gel Lubricant (i.e., the PVP gel used to manufacture Macroplastique); (ii) fill needle with Macroplastique; (iii) advance the cystoscope into the bladder, and insert the needle through the working channel; (iv) 1.5-2.0 distal from the bladder neck, insert the needle tip into the urethral tissue at the 6'o'clock position at a 30-45° angle, advance 0.5 cm, angle the scope to 0°, and advance another 0.5 cm; (v) inject ≤ 2.5 mL Macroplastique; (vi) wait 30 seconds after the injection before removing the needle to limit loss of Macroplastique through the injection site; and (vii) repeat the injection process at the 2 o'clock and 10 o'clock positions (injecting ≤ 1.25 mL per site; total injection volume ≤ 5.0 mL) to achieve mucosal coaptation. *Note*: The applicant has omitted the EZ-Gel priming step from the Macroplastique instructions for use, following comments from investigators that the needle can be directly filled with Macroplastique with equal reliability.

Following treatment, patients were prescribed prophylactic antibiotics and (if necessary) analgesia. Subjects who were able to void spontaneously were released. Instances of delayed voiding were managed using an intermittent catheter. Any patients unable to establish normal micturition within 48 hours were instructed to contact the investigator.

Patients in either study arm who were not dry and who desired a subsequent treatment were offered a single retreatment, administered no later than 4 weeks following the 3-month exam. For Macroplastique, retreatment was performed distal to the initial implant placement using the same guidelines as for the first implantation. For the control bulking agent, retreatment was performed followed standard medical practice.

Follow-Up Examination Schedule

All patients were scheduled for follow-up examinations at 1, 3, 6, and 12 months after final treatment. Additionally, Macroplastique subjects were scheduled to receive a 24-month evaluation to assess the long-term effects of treatment. The following data were collected at each of these examinations: pad weight test, 3-day incontinence diary, IQOL questionnaire, subject self-assessment/physician assessment of continence, and adverse event information. Additionally, cystoscopy was performed at the 12-month visit.

Patient Accountability

A total of 260 women were enrolled/randomized into the study (130 Macroplastique, 130 control), of whom 248 received treatment. The reasons that 12 enrolled subjects were not treated are: (i) subject cancellation/withdrawal (4 Macroplastique, 2 control); (ii) subject not a candidate for the study (2 Macroplastique, 2 control); and (iii) the investigator transferred institutions (2 Macroplastique). Subject enrollment began November 17, 1999, and all follow-up data received by July 18, 2005 are reported.

Of the 248 patients who received treatment, 197 (102 Macroplastique, 95 control) completed 12-month follow-up, and an additional 23 (9 Macroplastique, 14 control) withdrew prior to 12 months to seek alternate treatment and are known treatment failures. Therefore, treatment outcome status at 12 months is known for 220/248 (88.7%) of the study population (111 Macroplastique, 109 control). Complete patient accountability information is described in Table 2.

Table 2. Patient Accountability at 12-Month Follow-Up

Status	**Macroplastique** (n=130)	**Control** [1] (n=130)
Completed 12-month exam	102 (78.5%)	95 (73.1%)
Not implanted	8 (6.2%)	4 (3.0%)
Withdrew to seek alternate treatment	9 (6.9%)	14 (10.8%)
Withdrew for other reasons	4 (3.0%)	7 (5.4%)
Lost-to-follow-up	6 (4.6%)	8 (6.2%)
Missed 12-month exam	-	2 (1.5%)
Death	1 (0.8%)	-

[1] One subject randomized to the control bulking agent was implanted with Macroplastique.

Twenty-one percent of the study population was enrolled at the two Canadian sites. The Canadian sites followed the same protocol and used the same device formulation as the U.S. sites. Although these foreign data do not form the sole basis for marketing approval, they comply with all of the requirements listed under 21 CFR 814.15(d), such as: (i) being applicable to the U.S. population and medical practice; (ii) having

been collected by clinical investigators of recognized competence; and (iii) being available for on-site inspection.

A total of 883 protocol deviations were documented during the study (470 Macroplastique, 413 control). Analysis of these deviations found that less than 10% (i.e., n=87; 52 Macroplastique and 35 control) have the potential to affect study endpoints. These 87 deviations fall into the following categories: (i) missed 12-month visit; (ii) invalid/incomplete baseline or 12-month pad weight test; (iii) invalid/incomplete baseline or 12-month IQOL; (iv) blinding broken < 12 months; (v) randomization error; and (vi) missed visits/tests < 12 months post-treatment. Detailed review found that these 87 deviations will have minimal impact upon the study's primary conclusions, particularly since the primary analysis is based on the intent-to-treat population and the number of subjects enrolled exceeds the minimum required sample size. Also, these deviations were reasonably balanced between the study arms, and significant deviations (such as "missed 12-month visit") occurred in only a few subjects. Therefore, it is unlikely that these protocol deviations will alter the conclusions made in the PMA.

Demographic Data

Patients were adult females with a mean age of 61 years (ranging from 27 to 90 years). Table 3 displays the demographics and general baseline characteristics of the entire study population.

Table 3. Summary of Demographics and Baseline Characteristics

Characteristic	**Macroplastique** (n=128) [1]	**Control** (n=130)	**P-value**
Mean Age (yr.)	60.5	61.6	0.47
Race			0.81
Caucasian	95.3%	94.6%	
Hispanic	2.3%	3.8%	
African-American	1.6%	0.8%	
Asian	-	0.8%	
Other	0.8%	-	
Previous Pregnancies			0.02
0	11.7%	10.0%	
1	19.5%	11.5%	
2	29.7%	32.3%	
3	23.4%	16.9%	
4	7.0%	16.9%	
≥ 5	8.6%	12.3%	
Post-Menopausal			0.98
Yes	72.6%	73.1%	
No	26.6%	26.9%	
Unknown	0.8%	-	
Hysterectomy History			0.91
Yes	52.3%	53.1%	
No	47.7%	46.9%	
Hormone Replacement Therapy			0.32
Yes	53.9%	60.0%	
No	46.1%	40.0%	
Duration of Incontinence (yr.)	11.3	11.0	0.83
Previous Treatments[2]			
Non-Surgical	93.8%	96.2%	0.38
Surgical	23.4%	23.8%	0.94
Baseline Symptoms[2]			
SUI	100%	100%	-
Nocturia	70.9%	64.6%	0.28
Urgency	54.7%	58.5%	0.54
Frequency	52.3%	52.3%	1.00
Urge Incontinence	46.9%	51.5%	0.45
Incomplete Bladder Emptying	31.5%	27.1%	0.44
UTI	21.1%	27.9%	0.21
Enuresis	17.2%	9.3%	0.06
Hesitancy	8.7%	8.5%	0.97
Dysuria	1.6%	8.5%	0.01
Kidney Infection	7.4%	5.0%	0.47
Hematuria	1.6%	7.8%	0.02
Retention	2.3%	5.4%	0.20
Mean VLPP (cm H_2O)	65.6	64.1	0.51

[1] Baseline information not reported for 2 patients randomized to Macroplastique but never implanted.

[2] Subjects may appear in multiple categories.

The treatment groups are closely matched with regard to the majority of demographic and baseline factors. Analysis of baseline usage of medications that affect the bladder found no significant differences between the treatment groups. Control subjects had a significantly higher incidence of pre-existing dysuria and hematuria. However, only dysuria remained significant under Hochberg's multiple comparison adjustment. Dysuria was included in a logistic model, and not found to be a significant predictor of study success.

Table 4 summarizes the baseline incontinence status for the study population.

Table 4. Summary of Baseline Incontinence Status

Endpoint	Macroplastique	Control	P-value
Stamey Grade Distribution[1]			0.58
0	-	-	
1	30.2%	39.2%	
2	68.3%	53.8%	
3	1.6%	6.9%	
Mean Pad Weight (g)[2]	27.9	28.2	0.96
Mean IQOL Score[3]	49.3	48.2	0.70

[1] Baseline Stamey Grade is unavailable for 4 Macroplastique subjects.
[2] Baseline pad weight is unavailable for 2 Macroplastique subjects.
[3] Baseline IQOL is unavailable for 9 Macroplastique and 4 control subjects.

Nearly all patients (96.7% Macroplastique, 93.5% control) reported an average daily pad use of ≥ 1 pad/day, approximately half of whom reported use of 1-2 pads/day.

Data Analysis and Results

Treatment

Table 5 summarizes the treatment-related data for the complete study population. The number of treatments administered was similar for the two treatment groups, with slightly over half of subjects receiving retreatment.

Table 5. Treatment Information

Parameter	Macroplastique (n=122)	Control (n=126)
Number of Treatments		
1	47.5%	41.3%
2	52.5%	58.7%
Average Volume Injected at Initial Treatment (mL)	4.6	4.6
Average Volume Injected at Retreatment (mL)[1]	4.3	4.5
Total Volume of All Treatments (mL)	6.8	7.2

[1] Retreatments were administered to 138 subjects (64 Macroplastique, 74 control).

Macroplastique and control bulking agent treatments were typically performed under local anesthesia (69.7% Macroplastique, 84.9% control). The remaining subjects received either general anesthesia, conscious sedation, or nothing. As required by the protocol, all injections were delivered transurethrally. In both study arms, the majority of treatments involved injecting implant material at three sites within the urethra.

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Effectiveness

Improvement in continence, as measured by Stamey Grade, pad weight, IQOL, and physician and patient assessment are assessed for one or more of the following study populations:

(i) "Intent-to-Treat" (130 Macroplastique, 130 control) – all enrolled subjects, treating all patients without 12-month data as "failures;"
(ii) "Per Protocol" (122 Macroplastique, 125 control) – excludes patients who were either not implanted (n=12) or misrandomized (n=1); other patients without 12-month data treated as "failures;"
(iii) "Censored" (111 Macroplastique, 108 control) – excludes (i) all patients without 12-month data except those who left the study to seek alternate treatment (classified as "failures"), and (ii) the misrandomized subject; and
(iv) "As Followed" (number of subjects varies for each endpoint) – includes only those patients who were followed at the follow-up duration of interest (e.g., 6 months, 12 months).

For the statistical assessment of non-inferiority (i.e., "equivalence") for Stamey Grade improvement, p-values for Blackwelder's test at a delta of 15% are reported, consistent with the protocol. For the comparison of the other effectiveness endpoints, mean values are assessed for statistical significance, and (if applicable) the upper 95% confidence limits of the differences in success proportions are calculated. Additionally, the proportions of subjects with an improvement in Stamey Grade and pad weight were compared in a longitudinal model across all visits through 12 months. Finally, the applicant performed a logistic regression analysis for the endpoint of improvement in Stamey Grade at 12 months to evaluate the potential impact of various covariates upon the study conclusions.

The primary success criterion is improvement of at least one Stamey Grade at 12-month follow-up, compared to baseline grade. For each of the patient populations defined in the protocol, Macroplastique is statistically equivalent to the control bulking agent at the 15% delta level with respect to Stamey Grade improvement. Table 6 summarizes the primary and key secondary 12-month effectiveness results. Consistent with the study hypothesis, these analyses are based on the intent-to-treat study population.

Table 6. Key Effectiveness Results at 12 Months (Intent-to-Treat)

	Macroplastique	Control[1]	P-value[2]
Stamey Grade			
Dry	34.6% (45/130)	23.8% (31/130)	-[3]
Improvement of ≥ 1 grade[4]	57.7% (75/130)	46.9% (61/130)	< 0.001
Same	19.2% (25/130)	24.6% (32/130)	-
Worse/unable to assess[5]	23.1% (30/130)	28.5% (37/130)	-
Pad Weight			
≥ 50% improvement	60.0% (78/130)	53.1% (69/130)	-[3]
0-49% improvement	6.9% (9/130)	7.7% (10/130)	-
Worse/unable to assess[5]	33.1% (43/130)	39.2% (51/130)	-

[1] Includes one subject randomized to control but inadvertently implanted with Macroplastique. Since this subject's treatment was successful, the patient was analyzed as a success for the control bulking agent.

[2] Blackwelder test for equivalence, delta = 15%.

[3] Upper 95% confidence limit of the difference in proportions (control minus Macroplastique) is < 15%.

[4] Primary endpoint.

[5] Subjects without 12-month results are categorized as "worse."

To support the robustness of the primary effectiveness conclusion, sensitivity analyses were performed using a variety of methods to impute missing 12-month Stamey Grade results. These additional analyses further support the conclusion that Macroplastique is statistically equivalent to the control bulking agent with respect to Stamey Grade improvement.

Key secondary effectiveness endpoints were (i) dryness (i.e., Stamey Grade = 0) and (ii) improvement of ≥ 50% in pad weight. As with Stamey Grade improvement, these endpoints are assessed 12 months following last treatment. As shown in Table 5, Macroplastique is equivalent to the control bulking agent for each of these endpoints.

At each interim follow-up period (i.e., 1, 3, and 6 months), the proportion of subjects reporting improvement in Stamey Grade was equivalent between the two study arms (Macroplastique and control). Although longitudinal analysis of Stamey Grade improvement across all visits through the 12-month follow-up (adjusted for baseline Stamey Grade and visit) yielded odds of improvement in favor of Macroplastique over control (odds = 1.41), this result was not statistically significant. Therefore, the impact of Macroplastique treatment on Stamey Grade improvement during the 12 months follow-up period is similar to that of the control bulking agent.

Logistic regression was performed to assess the impact of baseline, demographic, and treatment factors upon Stamey Grade improvement, including (i) age, (ii) prior incontinence surgery, (iii) prior hysterectomy, (iv) use of medications that could potentially affect the bladder, (v) duration of incontinence, (vi) parity, (vii) baseline Stamey Grade, (viii) baseline pad weight, (ix) number of treatments, (x) clinical site, and (xi) U.S. versus Canadian sites. No statistical evidence was found to indicate the odds of treatment success for Macroplastique versus control are different across these subgroups.

Among subjects with baseline and 12-month pad weight data, mean pad weight reductions of 25.4 g and 22.6 g were observed for the Macroplastique and control arms, respectively. As with Stamey Grade, longitudinal analysis of pad weight improvement across all visits through the 12-month follow-up (adjusted for baseline pad weight and visit) yielded odds of improvement in favor of Macroplastique over control (odds = 1.55); however, this result was not statistically significant.

The quality of life of patients in the two study arms was compared using the IQOL questionnaire. In the Macroplastique group, mean IQOL improved from 49.3 points at baseline to 80.0 points at 12 months. This corresponds to a mean improvement of approximately 60%. A similar degree of improvement was observed among control subjects.

At the 12-month follow-up exam, subjects were asked to provide a subjective self-assessment of their degree of improvement (i.e., "cured/dry," "markedly improved," "slightly improved," or "unchanged"). One-third of Macroplastique subjects rated themselves as "cured" and another 44.1% rated themselves as "markedly improved," as compared to 26.3% and 42.1% (respectively) of control subjects. Approximately half of Macroplastique patients reported using pads at 12 months, with 75% of these patients reporting less pad usage than at baseline.

Similar to the patient self-assessment discussed above, investigators also provided a subjective rating of the improvement of each patient at 12 months (i.e., "cured/dry," "markedly improved," "slightly improved," or "unchanged"). Treating physicians rated 42.2% of Macroplastique patients as "cured" and another 38.2% as "markedly improved," as compared to 33.7% and 41.2% (respectively) of control subjects. Although the patient self-assessment was a blinded evaluation, the physician assessment was not.

Per the protocol, Macroplastique subjects were scheduled for additional follow-up 24 months following the last injection. At the time of database closure, 84/129 (65.1%) subjects received 24-month follow-up. Of these 84 subjects, 63 reported Stamey Grade improvement 24 months post-treatment (from baseline), of whom 28 were dry. Evaluating these results using an intent-to-treat approach, conservative estimates of the 24-month rates of Stamey Grade improvement and dryness are 48.8% (63/129) and 21.7% (28/129), respectively. However, since 35% of Macroplastique subjects were not assessed at 24 months, valid conclusions regarding the long-term effectiveness of Macroplastique cannot be drawn from these data.

Safety

The primary safety endpoint is comparison of the incidence and severity of adverse events between the Macroplastique and control arms. This analysis is based on the "per-protocol" population (122 Macroplastique, 125 control).

Adverse events were categorized as "treatment-related" (i.e., device or procedure-related) or "not treatment-related." To be conservative, all genitourinary adverse events, transient symptoms, and post-procedure catheterizations were classified as "treatment-related." A total of 96 Macroplastique subjects reported 303 treatment-related adverse events, versus 267 events among 90 control subjects. This difference

is not statistically significant. Table 7 lists the treatment-related adverse events in both groups.

Table 7. Number (%) Subjects Reporting Treatment-Related Adverse Events

Event Category	**Macroplastique** (n=122)	**Control** (n=125)
Post-procedure catheterization	53 (43.4%)	30 (24.0%)
Urinary tract infection (UTI)	31 (25.4%)	31 (24.8%)
Urinary retention	26 (21.3%)	18 (14.4%)
Dysuria	23 (18.9%)	15 (12.0%)
Hematuria (including transient hematuria)	19 (15.6%)	9 (7.2%)
Pain at implantation site	16 (13.1%)	16 (12.8%)
Frequency	14 (11.5%)	12 (9.6%)
Urgency	14 (11.5%)	9 (7.2%)
Slowed urine stream	9 (7.4%)	11 (8.8%)
Incomplete bladder emptying	7 (5.7%)	6 (4.8%)
Urge incontinence	7 (5.7%)	6 (4.8%)
Hesitancy	6 (4.9%)	9 (7.2%)
Vaginal bleeding	4 (3.3%)	1 (0.8%)
Yeast infection	4 (3.3%)	3 (2.4%)
Bladder pain	3 (2.5%)	4 (3.2%)
Cystitis	3 (2.5%)	-
Increased/worsening nocturia	3 (2.5%)	2 (1.6%)
Overactive bladder (OAB)	3 (2.5%)	-
Other[1]	29 (N/A)	41 (N/A)

[1] "Other" treatment-related adverse events in Macroplastique subjects, occurring at frequencies of < 2%, were as follows (listed alphabetically): abdominal pain, allergic reaction – control bulking agent skin test, bolus ruptured, change in urine stream, diarrhea, dizziness, filling defect, headache, increased AM urge incontinence, joint pain during urination, nausea, partial urethral closure, pelvic tenderness, perineal discomfort/pain, sleep disturbance, spotting between periods, tiredness, urethral erosion, uterine polyp, vaginal discharge, vaginal itching, visible product, and vulvar lesion.

With one exception, the rates of treatment-related adverse events are similar between the Macroplastique and control groups. The one notable difference in the frequency of treatment-related adverse events between Macroplastique and control groups is the occurrence of post-procedure catheterization, which is significantly higher among Macroplastique-treated subjects (43.4% Macroplastique, 24.0% control). The majority of these catherizations involved the use of an intermittent ("in/out") catheter immediately post-treatment (i.e., in the clinic), and were performed to drain the bladder at the end of the procedure either in response to transient episodes of delayed voiding or as a result of the anesthesia. This imbalance in the catheterization rate was limited to the initial treatment (32.8% Macroplastique, 13.5% control); following retreatment, the rates of catheterization were similar (approximately 30% per arm). The need for in/out catheterization immediately post-treatment was typically transient and self-resolving. Only one Macroplastique subject required an indwelling catheter after discharge, which was successfully removed after 48 hours. Given the low prevalence of post-discharge catheterization and the resumption of normal voiding in these patients, this event is not a serious safety issue.

Three cases of urethral erosion were observed in the clinical study, two in the Macroplastique arm and one in the control arm. For the erosions in the Macroplastique arm, neither case was reported due to patient complaint. Rather, both were observed during regular patient follow-up by study-related cystoscopy. One of these cases was documented to have healed spontaneously (on subsequent cystoscopy), while the other case was not evaluated on follow-up cystoscopy and is listed as having unknown resolution status.

Most treatment-related adverse events occurred in the first 30 days following treatment. At the time of database closure, all but 30 treatment-related adverse events in the Macroplastique arm were documented to have resolved. The following events were persistent or had unknown resolution status at the time of database closure (listed alphabetically with the number of events shown in parentheses): abdominal pain (n=1), bladder infection (n=1), bladder infection symptoms (n=1), change in urine stream (n=2), dysuria (n=2), filling defect (n=1), frequency (n=1), hesitancy (n=2), incomplete bladder emptying (n=2), overactive bladder (n=1), pelvic tenderness (n=1), spotting between periods (n=1), sleep disturbance (n=1), slowed urine stream (n=2), tenderness at implant site (n=1) transient hematuria (n=2), urethral erosion (n=1), urgency (n=3), urge incontinence (n=3), and vaginal discharge (n=1).

One Macroplastique subject died during the study. This death was attributed to complications of breast cancer, and was deemed unrelated to the device or the implantation procedure. There were no serious unanticipated adverse device effects reported in the Macroplastique arm.

Logistic regression was performed to assess the impact of baseline, demographic, and treatment factors upon the incidence of one or more treatment-related adverse event, including (i) age, (ii) prior incontinence surgery, (iii) prior hysterectomy, (iv) use of medications that could potentially affect the bladder, (v) duration of incontinence, (vi) parity, (vii) baseline Stamey Grade, (viii) baseline pad weight, (ix) number of treatments, (x) clinical site, and (xi) U.S. versus Canadian sites. No statistical evidence was found to indicate the odds of experiencing a treatment-related adverse event for Macroplastique versus control bulking agent are different across these subgroups.

Device Failures and Replacements

There were no device failures during the study.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

The preclinical data adequately characterize the device's materials, demonstrate that Macroplastique is safe for implantation in the urethral submucosa, and support a 2-year shelf life.

The clinical data demonstrate that Macroplastique treatment has a reasonable assurance of safety and effectiveness. In an intent-to-treat analysis of Macroplastique subjects, improvement in continence was achieved at 12 months in 57.7% of patients. Using this same dataset, dryness was achieved in 34.6% of Macroplastique patients. Twelve

months following treatment with Macroplastique, 60.0% experienced ≥ 50% reduction in urine leakage in the 1-hour pad weight test. Additionally, Macroplastique subjects experienced a mean IQOL improvement of approximately 60%. These results are statistically equivalent to those of the control population.

With the exception of post-procedure catheterization, the rates and severity of adverse events observed in the Macroplastique and control groups are similar to one another. Overall, adverse events associated with the use of Macroplastique were generally transient and minor. There were no reports of serious unanticipated adverse device events or patient deaths related to the use of Macroplastique.

Therefore, it is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Gastroenterology and Urology Devices Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

Based upon its review of the PMA, CDRH concludes that these data provide reasonable assurance that Macroplastique is safe and effective when used in accordance with the directions for use. Therefore, the PMA is approved, subject to the requirements that

- Uroplasty, Inc. perform a 5-year postapproval study to assess the long-term safety and effectiveness of Macroplastique (e.g., durability of the treatment effect, the impact of retreatment); and
- Uroplasty, Inc. conduct a 2-year enhanced surveillance program, in which U.S. physicians using Macroplastique will be contacted on a quarterly basis to actively solicit information on adverse events.

In Amendment 6, received by FDA on September 19, 2006, Uroplasty submitted these postapproval study plans.

FDA issued an approval order on October 30, 2006.

The applicant's manufacturing facilities were inspected September 7-14, 2006, and were found to be in compliance with the Quality System Regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See the labeling.

Hazards to Health from Use of the Device: See Indications for Use, Contraindications for Use, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.

XV. REFERENCES

1. "Use of International Standard ISO 10993-1, 'Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing'," FDA, CDRH, May 1, 1995, (http://www.fda.gov/cdrh/g951.html).

2. Stamey T, "Urinary Incontinence in the Female," in Campbell's Urology, Fourth Edition, Philadelphia, W. B. Saunders Company, pp. 2272-2293, 1979.

3. Wagner TH, Patrick DL, et al., "Quality of Life in Persons with Urinary Incontinence: Development of a New Measure," Urology, 47(1), pp. 67-72, 1996.