SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Injectable Bulking Agent
Device Trade Name:	URYX® Urethral Bulking Agent
Applicant's Name and Address:	Genyx Medical, Inc. 66 Argonaut, Suite 170 Aliso Viejo, California 92656
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P030030
Date of Notice of Approval to Applicant:	December 16, 2004

II. INDICATIONS FOR USE

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

III. CONTRAINDICATIONS

URYX is contraindicated in patients with the following conditions:

- acute cystitis, urethritis, other acute or chronic genitourinary tract infections, or
- fragile urethral mucosal lining.

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

URYX is a permanently implanted, non-pyrogenic, injectable bulking agent composed of ethylene vinyl alcohol (EVOH) copolymer dissolved in dimethyl sulfoxide (DMSO). The resulting mixture is approximately 8% EVOH in DMSO. URYX is packaged in 3 mL glass vials and dry heat sterilized. Each vial is sold with a sterile, 3 cc syringe. The syringe is DMSO-compatible, and comes with a drawing needle (20 gauge by 1 inch). Injection of URYX is accomplished using a legally marketed, 25 gauge needle (supplied separately).

URYX is injected into the urethral submucosa approximately 2 cm distal to the bladder neck. Following injection into the tissue, the DMSO diffuses away, resulting

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in the EVOH forming a solid, spongy mass. The injection of URYX 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

URYX is currently marketed in England and Switzerland. URYX 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 174 patients implanted with URYX in a multicenter, prospective study. All study patients were adult women diagnosed as having SUI due to ISD. A total of 583 adverse events were reported during the clinical trial, of which 437 were categorized as being related to either the device or treatment (referred to as "treatment related"). One hundred twenty-six (126) of the 174 patients receiving treatment (72.4%) 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." There were no deaths or serious unanticipated adverse device effects.

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

Event Category	**URYX** (n=174)
Urinary tract infection (UTI)	50 (29%)
Delayed voiding	32 (18%)
Dysuria	31 (18%)
Exposed material	28 (16%)
Urinary urgency	24 (14%)
Urinary frequency	22 (13%)
Genitourinary (infection, tenderness)	20 (11%)
Hematuria	19 (11%)
Urge incontinence	16 (9%)
Worsening of incontinence (onset of urge)	14 (8%)
Outlet obstruction	13 (7%)
Pain at injection site	13 (7%)
Pelvic pain	13 (7%)
Yeast infection	12 (7%)
Leakage of urine/stress incontinence	9 (5%)
Bulking material injected into bladder	7 (4%)
Fatigue	3 (2%)
Abnormal urinalysis	3 (2%)
Bladder fullness	3 (2%)
Nocturia	3 (2%)
Pelvic heaviness	3 (2%)
Uterine fibroids	3 (2%)

Most treatment related adverse events occurred within 24 hours of treatment and subsequently resolved within 30 days. At the time of database closure, 92% of treatment related adverse events were resolved. The following events were persistent or resolution was unconfirmed at the time of database closure (the number of events is shown in parentheses): urge incontinence (6); leakage of urine/stress incontinence (5); worsening of incontinence (onset of urge) (5); exposed material (4); uterine fibroids (3); urinary tract infection (2); urinary frequency (2); urinary urgency (2) and one event each of genitourinary (infection/tenderness), kidney stones, nocturia, pelvic pain, urethral redness, and URYX removal.

With respect to severity of the treatment related adverse events:

- 172 (39.4%) were rated as mild;
- 251 (57.4%) were rated as moderate; and
- 14 (3.2%) were rated as severe.

The physician investigators reported 14 events in 10 subjects as severe: 3 cases of exposed material; 2 cases each of bulking material injected into the bladder, delayed voiding, and urge incontinence; and 1 case each of bladder spasms, bladder stones, hematuria, pelvic pain, and urinary frequency. With the exception of one case of urge incontinence, all severe treatment related events were documented to have resolved.

Patients experiencing exposed material often reported other events, particularly dysuria, delayed voiding, urinary tract infection, hematuria, urinary frequency, and urinary urgency. Exposed URYX material was associated with shallow placement and

injection too proximal to the bladder neck. Over time, the urethra healed spontaneously as the mucosal surface re-epithelialized. Some physicians chose to remove exposed material cystoscopically with graspers or forceps to facilitate healing.

The majority of patients were injected via the transurethral approach, while a small proportion of patients were injected periurethrally. There were significantly more adverse events among URYX patients treated periurethrally; as a result, the URYX instructions for use are limited to transurethral administration.

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 erosion erythema, embolic phenomena, 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 URYX (final, sterilized samples) and its constituent materials (EVOH copolymer, DMSO). The specific studies that were performed are as follows:

Chemical Analyses
- Gel permeation chromatography (URYX & EVOH)
- Fourier transform infrared spectroscopy (URYX, EVOH & DMSO)
- Gas chromatography/mass spectroscopy (URYX, EVOH & DMSO)
- Heavy metals analysis (EVOH)
- Differential scanning calorimetry (EVOH)

Physical Testing
- Viscosity (URYX)
- Solidification in aqueous solution (URYX)
- Injection force (URYX)

The chemical analyses confirmed the identity and purity of the EVOH and DMSO used in URYX. The physical tests verified that the URYX can be easily injected (< 3 lbs force, versus > 6 lbs force for legally marketed injectable bulking agents for incontinence), and that injection in an aqueous environment resulted in the formation of a solid mass. These chemical analyses and physical tests verified that the product conforms to design specifications, and demonstrated product consistency between lots.

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), and "Draft Guidance for Preclinical and Clinical Investigations of Urethral Bulking Agents

Used in the Treatment of Urinary Incontinence."[2] Testing was carried out in compliance with 21 CFR Part 58, "Good Laboratory Practice for Nonclinical Laboratory Studies." This testing included:

- cytotoxicity (MEM elution),
- sensitization by guinea pig maximization (Magnusson/Kligman),
- intracutaneous reactivity,
- acute systemic toxicity,
- subacute toxicity,
- acute rabbit intramuscular implant (7-day), and
- genotoxicity testing (bacterial reverse mutation, mouse lymphoma forward mutation assay, and mouse micronucleus test).

Except for the (i) acute systemic toxicity and (ii) 7-day intramuscular implant test, the material met the test requirements. The results of these two tests are as follows:

(i) In the acute systemic toxicity testing, URYX extracts of saline and cotton seed oil (CSO) were injected into 10 mice (5 mice per group). Ten additional mice served as negative controls and received blank saline and CSO extracts (5 mice per group). Of the 5 mice that received CSO extracts of URYX, 2 died and 2 lost weight. The remaining test animals (saline and CSO extracts) were observed to have signs of toxicity 15 minutes after injection (i.e., lethargy, lack of muscle tone, tremors, twitches, spasms, staggering gait), all of which resolved within 4 hours. Based on these results (primarily the two deaths), URYX failed to meet the requirements of the USP acute systemic toxicity test. In repeat testing, no deaths occurred and all animals that received the CSO extract gained weight. However, transient toxic reactions continued to be observed. These reactions were attributed to the DMSO dose that was administered with the extract, which was approximately 200 times greater than that delivered in a URYX treatment. Since similar transient symptoms were not reported in the URYX clinical trial, the findings in these mice are not believed to be clinically significant.

(ii) In the 7-day intramuscular implantation testing, histopathological examination revealed that the test article caused a greater local effect, compared to the control. The test article sites demonstrated severe necrosis, marked infiltrations of macrophages, a moderate to marked foreign body reaction, vascularization and fibrosis, and some mineralization. This acute reaction was primarily attributed to the presence of the DMSO, which is a known dehydrating agent. On the basis of the histopathological observation, URYX failed to meet the requirements of the 7-day USP muscle implantation test. Although URYX failed the acute muscle implantation test, the histopathology results from the chronic toxicity studies (discussed below) demonstrate that the greatest inflammation occurs by Day 30. Following this time point, the acute inflammation stabilizes to a mild, localized, foreign body response.

Chronic Toxicity Studies

Chronic toxicity studies were performed to evaluate the long-term effects of URYX implantation. These chronic toxicity studies involved (i) muscle implantation in rabbits, and (ii) periurethral implantation in swine. The findings of these tests are summarized as follows:

(i) Intramuscular implantation was performed in New Zealand white rabbits to evaluate the long-term response of tissues to URYX. Histology was performed on animals sacrificed at 1, 3, 6, 9, and 12 months. Implantation of URYX resulted in an acute

inflammatory response occurring early, then developing into a chronic inflammatory response. Histopathology of the implantation sites showed that the greatest severity of inflammation occurred at 1 month. After 3 months, the severity of the inflammatory response decreased, stabilized, and was generally characterized as a mild, localized, foreign body response with some mineralization. There was no evidence of either implant effects on tissues away from the implant site, or migration of the implanted material.

(ii) A swine study was performed to simulate clinical use conditions of URYX with regard to cystoscopic delivery, implant site, and volume of material injected. A total of 36 minipigs received a minimum of two injections of URYX (containing tantalum powder, added for radiopacity) into the urethral wall. Animals were sacrificed at 48 hours, 7 days, and 1, 3, 6, 9, 12, 20 and 24 months post-implantation. In addition to histologic examination of the urethra and implant sites, histology was performed on all major organs (i.e., brain, kidney, liver, lung, lymph nodes, spleen, and urinary bladder). The histological assessment at the injection sites demonstrated evolution of the tissue response from acute inflammation (at 48 hours and 7 days), through a sub-acute inflammatory process accompanied by increased fibrosis (at 1-3 months), to a stable foreign body response with a slight reduction in fibrosis and some mineralization (6-24 months). These findings were considered to be consistent with an expected progress of reaction and subsequent healing at an implantation site. The presence of mineralization within urethral submucosa was not believed to be clinically significant. Histological examination of the major organs and distant sites revealed neither signs of systemic toxicity nor evidence of migration.

Carcinogenicity Testing

Carcinogenicity testing was conducted by the sponsor using the *ras*H2 transgenic mouse model. Based on the results of the study, URYX was found to be non-carcinogenic in the *ras*H2 transgenic mouse.

Sterilization Testing

Vials of URYX are sterilized using a dry heat sterilization process. The process was validated to ensure a sterility assurance level of at least 10^{-6}.

Package Integrity/Shelf Life Studies

Studies were performed to confirm the integrity of the URYX packaging and to support claims of an extended shelf life. The findings of these tests are summarized as follows:

- Package integrity testing: Environmental and transportation testing verified that the conditions of transportation, temperature variation, and humidity changes did not affect the integrity of the glass vials or outer box. However, the URYX-filled glass vials could not withstand temperatures below 0°C. Based on the conditions of this testing, product is labeled "Do Not Freeze."
- Shelf life testing: Accelerated aging testing on URYX supports a shelf life claim of 36 months.

X. SUMMARY OF CLINICAL STUDIES

Objectives

A clinical study was conducted under IDE G980325. The objectives of the clinical trial were to assess the safety and effectiveness of URYX in the treatment of female SUI due to ISD, and to demonstrate equivalence to a currently marketed absorbable bulking agent ("control").

Study Design

Overview

The study was a multicenter, masked, randomized, controlled trial conducted at 15 institutions (11 U.S. and 4 Canada). Female patients with SUI due to ISD were randomized (2:1) to either URYX or control. Following treatment, patients in both arms were assessed at regular intervals over a 12-month period. The U.S. and Canadian sites followed the same protocol.

The study was phased such that the initial 41 patients were enrolled at 3 clinical sites. Expansion of enrollment to the full study population was performed based on evaluation of the 3-month outcomes of the first 15 patients (10 URYX, 5 control). These two study phases are referred to as the feasibility and expansion phases, respectively.

The design of this clinical study is consistent with the recommendations of the FDA guidance document "Draft Guidance for Preclinical and Clinical Investigations of Urethral Bulking Agents Used in the Treatment of Urinary Incontinence."

Patient Selection

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

- Female, age ≥ 18 years
- Valsalva Leak Point Pressure (VLPP) ≤ 100 cm H_2O
- Duration of incontinence > 12 months
- Failed prior treatments for SUI
- Normal bladder capacity (250-500 mL)
- Viable mucosal lining at the injection site

The exclusion criteria were:

- Types of incontinence other than SUI
- Uncontrolled bladder instability
- Medications for urinary incontinence other than anticholinergics
- Uterine prolapse > Stage II
- Post-void residual urine volume > 60 mL
- History urethral strictures, bladder neck contracture, or potentially confounding bladder pathology
- Current use of intravaginal pessaries
- Morbid obesity (> 100 lbs over ideal body weight)
- Positive urine culture

- Concurrent infection (e.g., cystitis, urethritis, or vaginitis)
- Chronic disease that would interfere with the patient's safety or ability to comply with the protocol (e.g., uncontrolled diabetes, malignancy, major organ illness, immunocompromised status)
- Allergy to bovine collagen products
- Concurrent or planned desensitization injections to meat products
- Autoimmune disease or history of severe allergic reactions
- Previous implantation of a urethral bulking agent
- Pregnant, actively lactating, planning to become pregnant in next 12 months, or of child-bearing potential and not practicing a medically approved method of birth control

Hypothesis/Sample Size

The primary endpoint for determining the sample size 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 the proportion of URYX patients successfully meeting the primary endpoint is no worse than that observed in the control arm minus some maximum allowable difference (δ). A sample size of 165 patients was calculated (110 URYX, 55 control), based on a non-inferiority (i.e., 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) = 0.20
P1 = P2 = 0.50-0.80 (expected success based on the primary endpoint)

The protocol specifies that the primary comparisons of URYX effectiveness will be based on available data at last follow-up visit, imputing missing data using "last observation carried forward" (LOCF). Since the effectiveness of URYX does not degrade over the 12-month follow-up period, the use of this imputation method in this study does not bias the results in favor of URYX.

Primary Effectiveness Endpoint

Stamey Grade

The primary effectiveness endpoint for the study was improvement (decrease) of ≥ 1 incontinence grade from baseline to 12 months post-treatment. The incontinence grading scale used for this study was defined by Stamey in 1979[3], 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. This evaluation was performed during follow-up visits to the physician's office. Prior to testing, the patient's bladder was filled with 250 mL of saline or water using a small catheter. The test involved the patient wearing a pre-weighed pad while she completed a prescribed set of physical activities, after which the pad was weighed again. Pad weight improvement was defined as a decrease in pad weight of $\geq 50\%$ from baseline. For this measurement, patients with urine loss of ≤ 2 grams were defined as dry. The percentages of patients meeting the criteria for (i) dry and (ii) improved on pad weight were reported for each follow-up interval.

Incontinence Quality of Life (IQOL) Questionnaire

The IQOL questionnaire is a validated instrument consisting of 22 questions[4]. 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.

Valsalva Leak Point Pressure (VLPP)

VLPP is the intra-abdominal pressure at which urine leakage occurs, and is an indirect measure of sphincteric weakness. Although the study protocol lists VLPP as a secondary outcome measure, this urodynamic parameter was not assessed at follow-up in the majority of patients due to the subjects' unwillingness to be catheterized for this invasive urodynamic test. Using the available data, mean VLPP measurements were reported and compared.

Safety Endpoints

Safety was evaluated by comparing the incidence and severity of complications and adverse events for the URYX and control treatment arms, as well as the results of cystoscopic evaluations.

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 (including VLPP), pad weight test, 3-day incontinence diary, IQOL questionnaire, blood work, urinalysis, and the skin sensitivity test for the control bulking agent. Only those individuals satisfying the inclusion and exclusion criteria were randomized. On the day of treatment, prior to the bulking procedure, an initial cystoscopic examination was performed.

Treatment

Patients who did not demonstrate a response to the skin test within a 30-day observation period, and who were otherwise eligible for treatment, were injected with either URYX or the control bulking agent (as determined by block randomization). Treatments were performed on an outpatient basis under local anesthesia. Patients were blinded to the treatment they received (i.e., URYX or control).

URYX and the control bulking agent were delivered to the urethral submucosa (typically 1-2 sites) via either transurethral or periurethral injection techniques, depending upon investigator preference (each investigator was requested to use the same technique throughout the study). All treatments were performed under cystoscopic visualization.

Control treatments were performed according to the approved instructions for use. In the feasibility phase of the study, investigators were instructed to inject URYX using standard methods for urethral bulking procedures. In the subsequent expanded phase of the study, the URYX injection procedures were modified as described below under "Patient Accountability."

Prior to release, study patients were asked to sit upright and perform a task, such as cough, to check for leakage, and void on their own volition. Instances of delayed voiding were managed by catheterization.

Telephone interviews were conducted 1, 7, 14, 28, 42, 56, and 70 days following initial treatment to assess the patient's continence status and any complications. Any patient who indicated that dryness had not been achieved was asked to return for evaluation for retreatment. Patients in both study arms were permitted a maximum of two retreatments, for a total of three treatments. Retreatments were only permitted during the 90 day period following the initial treatment, and could be scheduled no sooner than 4 weeks from the prior treatment.

Follow-Up Examination Schedule

All patients were scheduled for follow-up examinations at 3, 6, and 12 months after final treatment. The following data were collected at each of these examinations: pad weight test, 3-day incontinence diary, IQOL questionnaire, and adverse event information. Additionally, VLPP was assessed at the 12-month visit.

Although study investigators could not be masked to each subject's treatment assignment, personnel who performed telephone surveys, administered quality of life questionnaires, and questioned study subjects for adverse events were masked.

Patient Accountability

A total of 260 women were enrolled into the study, of which 253 received treatment. The reasons that seven enrolled patients were not treated are: (i) incontinence improved prior to treatment (2 URYX), (ii) GI problem prior to treatment (1 control), (iii) delayed positive reaction to the control skin test (1 URYX, 1 control), (iv) pregnancy (1 URYX), and (v) unable to locate subject (1 URYX). The

253 treated patients consist of 16 URYX subjects enrolled in a non-randomized fashion (to give new investigators initial experience with URYX), and 237 patients randomized 2:1 between URYX and control. Patient enrollment began October 1999, and all follow-up data received by December 19, 2003, are reported.

The clinical trial was conducted in two phases – a feasibility phase, followed by an expansion phase. The feasibility phase consisted of 41 randomized subjects (28 URYX, 13 control) conducted at 3 U.S. and 3 Canadian sites. Review of the feasibility phase data observed a high incidence of material exposure at the implantation site in URYX patients. These events were attributed to the injection technique being used. During the feasibility phase, investigators followed the same injection procedures customary for the use of other injectable bulking agents, including: no limit on injection volume or rate of injection; placement proximal to the bladder neck; shallow placement; and complete coaptation of the urethra. Based on the feasibility results, the protocol was amended to revise the URYX injection instructions as follows: (i) inject ≥ 2 cm distal from the bladder neck; (ii) inject at an angle of 30-45° to avoid shallow placement; (iii) inject no more than 1.0 mL/site and 2.5 mL/treatment; (iv) inject slowly (i.e., 1 mL/min); and (v) hold the needle in the injection site for a minimum of 1 minute after the injection is completed.

The remaining 212 patients were enrolled at 15 sites in the expansion phase of the study. Based on the experience with URYX of the feasibility phase, it was determined that new investigators should treat the first two patients with URYX in a non-blinded, non-randomized fashion to give the investigator experience with the URYX injection technique. A total of 16 non-randomized patients were treated. The remaining 196 expansion phase subjects (130 URYX, 66 control) were treated in a randomized fashion.

The pooling of the feasibility and expansion phase patients is justified based on the following analyses: (i) logistic modeling did not identify study phase (feasibility vs. expansion) as a significant factor for URYX or control effectiveness; (ii) patients in the two study phases are similar with respect to completion status, relevant baseline characteristics (except baseline Stamey Grade), and outcome; and (iii) the inclusion of URYX feasibility patients with lower baseline Stamey Grade and higher adverse events will not bias the results in favor of URYX. (Note: This last point is based on the logistic modeling analysis, which demonstrated that lower baseline Stamey Grade is associated with a lower success rate.) By pooling study phases, the analysis of device safety is based on all 253 subjects (174 URYX, 79 control) who received treatment. However, the effectiveness analysis excludes the 16 non-randomized, expansion phase patients, resulting in 237 randomized patients (158 URYX, 79 control).

Of the 253 patients treated in the study, 177 (120 URYX, 57 control) received 12-month follow-up. Twelve-month data are unavailable for the remaining 76 subjects for the following reasons: (i) 51 (38 URYX, 13 control) discontinued either to seek alternative treatment (n=49) or due to an adverse event (n=2); (ii) 21 (13 URYX, 8 control) were lost to follow-up; and (iii) 4 (3 URYX, 1 control) were continuing in the study and not yet due for follow-up at the time of database closure. (Note: After database closure, the applicant submitted the 12-month results of the 4 ongoing patients. This additional information did not change the conclusions of either the primary effectiveness analysis or the safety assessment. Therefore,

reanalysis of the clinical results to include these additional data is not warranted.) Therefore, a total of 72/253 patients (28.5%) prematurely terminated the study (i.e., discontinued or lost to follow-up). The rate of premature termination is similar between study arms.

Approximately half of the study population was treated at the four Canadian sites (120/253; 47.4%). 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.

Protocol deviations occurred in 22 subjects (6 URYX, 16 control), consisting of 12 deviations from the inclusion/exclusion criteria and 10 procedural deviations. These deviations were minor, and did not result in the exclusion of any subject from the effectiveness analyses. Although disproportionally high among control subjects, the imbalance in protocol deviations between study groups did bias the results in favor of URYX.

Demographic Data

Patients were adult females with a mean age of 61 years (ranging from 30 to 91 years). Table 2 displays the demographics and general baseline characteristics of the entire study population.

Table 2. Summary of Demographics and Baseline Characteristics

Characteristic	URYX (n=174)	Control (n=79)	P-value
Mean Age (yr.)	60.9	61.0	0.942
Race			0.095
Caucasian	96.0%	91.1%	
African	2.3%	1.3%	
Hispanic	1.1%	3.8%	
Asian	0.6%	1.3%	
Other	-	2.5%	
Previous Pregnancies			0.866
0	9.8%	6.3%	
1-2	39.6%	40.5%	
3-4	36.8%	39.3%	
≥ 5	13.8%	13.9%	
Menopausal Status			0.630
Pre	13.8%	13.9%	
Peri	4.6%	7.6%	
Post	81.0%	78.5%	
Unknown	0.6%	-	
Hysterectomy History			0.845
None	43.1%	40.5%	
Abdominal	37.9%	41.8%	
Vaginal	19.0%	17.7%	
Duration of Incontinence (yr.)	9.6	9.9	0.750
Etiology*			
Childbirth Injury/Trauma	47.7%	44.3%	0.684
Surgery	20.1%	24.1%	0.510
Other Injury/Trauma	0.6%	1.3%	-
Medications	0.6%	-	-
Other	48.2%	54.4%	0.416
Previous Treatments*			
Behavioral	70.1%	70.9%	1.000
Drugs	47.7%	53.2%	0.498
Prior Surgery	44.8%	48.1%	0.684
Baseline Symptoms*			
Nocturia	55.2%	39.2%	0.021
Frequency	43.7%	31.6%	0.074
Urgency	35.1%	38.0%	0.673
Urge Incontinence	32.8%	30.4%	0.772
Straining	7.5%	3.8%	0.404
Poor or Interrupted Stream	6.9%	10.1%	0.451
Hesitancy	4.0%	3.8%	1.000
Dysuria	2.9%	2.5%	1.000
Suprapubic or Perineal Pain	2.9%	-	0.329
Hematuria	2.3%	-	0.313
Mean VLPP (cm H_2O)**	70.3	66.2	0.172

* Subjects may appear in multiple categories.

** Baseline VLPP only available for 246 subjects.

The treatment groups were similar with regard to the majority of demographic and baseline factors. However, URYX subjects had a significantly higher incidence of pre-existing nocturia (p=0.021). Additionally, the incidence of pre-existing of urinary frequency was slightly higher in the URYX group. Therefore, these two conditions were examined as possible factors in the logistic regression model. This analysis found no significant effect on either Stamey Grade or pad weight improvement due to these baseline conditions.

Table 3 summarizes the baseline incontinence status for the 237 randomized patients. The mean baseline Stamey Grade in each study arm is the same (i.e., 2.0).

Table 3. Summary of Baseline Incontinence Status

Endpoint	**URYX** (n=158)	**Control** (n=79)	**P-value**
Stamey Grade Distribution			0.638
0	-	-	
1	12.0%	15.2%	
2	71.5%	72.1%	
3	16.5%	12.7%	
Mean Pad Weight (g)*	32.0	28.2	0.517
Mean IQOL Score	63.1	58.4	0.098

* Baseline pad weight only available for 234 subjects (156 URYX, 78 control).

Data Analysis and Results

Treatment

Table 4 summarizes the treatment-related data for the complete study population. The number of treatments administered within the 90-day treatment window was similar for both treatment groups. Approximately three-quarters of subjects in each group received at least one retreatment. Of note is the fact that URYX subjects received significantly less bulking agent, both per treatment and overall, than control patients (p<0.001).

Table 4. Treatment Information

Parameter	**URYX** (n=174)	**Control** (n=79)
Number of Treatments		
1	23.6%	24.1%
2	37.9%	40.5%
3	38.5%	35.4%
Average Volume per Treatment (mL)	2.2	3.4
Total Volume of All Treatments (mL)	4.7	7.3

As permitted by the protocol, treatment was delivered via either transurethral or periurethral injection. The majority of subjects were treated via the transurethral approach (82% URYX, 87% control). Only one investigator injected URYX periurethrally.

Effectiveness

The effectiveness analysis is based on all randomized, treated subjects; i.e., 237 patients (158 URYX, 79 control). Improvement in continence, as measured by Stamey Grade, pad weight, and IQOL, was assessed in an intent to treat fashion using last observation carried forward (LOCF) to impute missing data. VLPP was analyzed as an effectiveness endpoint, but only for observed 12-month values. For Stamey Grade and pad weight improvement, sensitivity analyses and logistic modeling were also performed. The sensitivity analyses used a variety of methods to impute the outcomes of patients with missing 12-month data, and are intended to demonstrate the robustness of the results despite the relatively large percentage of missing data. For each statistical analysis, p-values for Blackwelder's test at a delta of 20% are reported, consistent with the protocol. To provide further support of the equivalence of URYX at the 20% delta level, the applicant also reports either (i) the p-value at an alternate delta level of 15% or (ii) the exact delta level corresponding to a p-value of 0.05.

The primary success criterion is improvement of at least one Stamey Grade at 12-month follow-up, compared to baseline grade. Consistent with the primary study hypothesis, this analysis is based on the entire randomized study population with all missing data imputed using LOCF. As shown in Table 5, URYX is equivalent to control at the 20% delta level with respect to Stamey Grade improvement (URYX success rate = 48.7%). However, equivalence does not hold at the alternate delta level of 15% (exact delta level = 15.7%), which is the maximum delta recommended by the Agency.

Table 5. Effectiveness Results at 12 Months (All Patients/LOCF)

	URYX	**Control**	**P-value***	**Exact Delta****
Stamey Grade				
Dry	18.4% (29/158)	16.5% (13/79)	<0.001	6.6%
Improvement of ≥ 1 grade***	48.7% (77/158)	53.2% (42/79)	0.012	15.7%
Same	47.5% (75/158)	36.7% (29/79)	-	-
Worse	3.8% (6/158)	10.1% (8/79)	-	-
Pad Weight				
Dry	37.8% (59/156)	32.1% (25/78)	<0.001	5.0%
≥ 50% improvement	50.0% (78/156)	48.7% (38/78)	0.001	10.1%
1 – 49% improvement	11.5% (18/156)	14.1% (11/78)	-	-
No improvement or worse	38.5% (60/156)	37.2% (29/78)	-	-
IQOL				
≥ 50% improvement	22.2% (35/158)	29.1% (23/79)	0.016	17.0%
≤ 50% improvement	77.8% (123/158)	70.9% (56/79)	-	-
Mean improvement	9 points	16 points	-	-

* Blackwelder test for equivalence, delta = 20%.
** Based on the one-sided 95% upper confidence limit for control – URYX.
*** Primary endpoint.

URYX and control patients had similar changes in mean Stamey Grade throughout the 12-month follow-up period. At 12 months, each group had a mean reduction of approximately 0.8.

The secondary effectiveness endpoints were: (i) improvement of ≥ 50% in pad weight; (ii) dryness (i.e., Stamey Grade = 0); (iii) dryness (pad weight ≤ 2 grams); and (iv) improvement of ≥ 50% in IQOL. As with Stamey Grade improvement, these endpoints are assessed 12 months following last treatment. As shown in Table 5, URYX is equivalent to each of these endpoints at the 20% delta level. For pad weight improvement and both measures of dryness, the results remain equivalent at the alternate delta level of 15%. However, for IQOL improvement, equivalence does not hold at the alternate delta level of 15%.

Among subjects with baseline and 12-month pad weight data, mean pad weight reductions of 18.0 and 2.4 g were observed for the URYX and control arms, respectively. This result is statistically significant in favor of URYX. However, statistical significance is not achieved when the LOCF imputation is applied to the entire population.

In addition to the analysis of the 12-month results, the rates of improvement and dryness were also compared at earlier time points (i.e., 3 and 6 months after final treatment). For Stamey Grade, these earlier comparisons are significant for equivalence at the 20% delta level, with the exception of improvement at 3 months. However, all 3- and 6-month pad weight comparisons meet both the 20% and 15% delta levels for equivalence. The results of repeated measures analysis (i.e., General Estimating Equations – GEE) for Stamey Grade and pad weight show that the URYX improvement rate increased from 3 to 12 months while control improvement stabilized at 3 months.

To support the robustness of the comparison of the LOCF results given the 28.5% missing data rate, sensitivity analyses were performed using a variety of methods to impute missing 12-month results. These analyses were separately performed for assessment of Stamey Grade improvement and pad weight improvement. These analyses include multiple imputation, repeated measures analysis (i.e., GEE), and a variety of LOCF imputations with various assumptions for failure (including all non-completers counted as failures). All of these additional analyses demonstrate the equivalence of URYX at the 20% delta level with respect to both Stamey Grade improvement and pad weight improvement. Furthermore, the majority of these analyses continue to support equivalence at the alternative delta level of 15%.

Logistic modeling identified the following baseline factors as having a significant impact on Stamey Grade and pad weight improvement: (i) baseline Stamey Grade (subjects with a higher baseline grade had a higher improvement rate across both treatment groups); and (ii) baseline pad weight (subjects with a higher baseline value had a higher improvement rate across both treatment groups). Additionally, the number of treatments was found to influence Stamey Grade improvement (i.e., subjects who received a single treatment had a higher improvement rate across both treatment groups). It is important to note that the following factors did not impact these endpoints: study phase (feasibility vs. expansion), injection method (transurethral vs. periurethral), and investigational site.

Although VLPP testing at the 12-month follow-up exam was a protocol requirement, only 28.5% (72/253, 47 URYX, 25 control) of subjects had this test performed. The applicant stated that this test was often not performed, particularly when the subject presented with a dry pad weight test or a Stamey Grade of zero. Furthermore, many

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subjects declined this test due to its invasive nature (i.e., catheterization). For the available data, URYX subjects reported an increase in VLPP from 70.3 cm H_20 at baseline to 79.7 cm H_20 at 12 months. A similar change was observed for control subjects. Due to the sparsity of the data, no conclusions can be drawn regarding VLPP change over time in this study population.

Safety

The primary safety endpoint is comparison of the incidence and severity of adverse events between the URYX and control treatment arms. This analysis is based on the entire cohort of 253 patients (174 URYX, 79 control). Overall, 82.8% of URYX subjects reported at least one adverse event, compared with 77.2% of control subjects. There were no deaths or serious unanticipated adverse device effects in either the URYX or control groups.

Table 6 lists all adverse events in both groups that were classified as related to the device or treatment ("treatment related"). To be conservative, all genitourinary adverse events were classified as "treatment related."

Table 6. Number (%) Subjects Reporting Treatment Related Adverse Events

Event Category	**URYX** (n=174)	**Control** (n=79)
Urinary tract infection (UTI)	50 (29%)	15 (19%)
Delayed voiding	32 (18%)	10 (13%)
Dysuria	31 (18%)	11 (14%)
Exposed material	28 (16%)	-
Urinary urgency	24 (14%)	7 (9%)
Urinary frequency	22 (13%)	9 (11%)
Genitourinary (infection, tenderness)	20 (11%)	10 (13%)
Hematuria	19 (11%)	5 (6%)
Urge incontinence	16 (9%)	4 (5%)
Worsening of incontinence (onset of urge)	14 (8%)	3 (4%)
Outlet obstruction	13 (7%)	4 (5%)
Pain at injection site	13 (7%)	4 (5%)
Pelvic pain	13 (7%)	7 (9%)
Yeast infection	12 (7%)	4 (5%)
Leakage of urine/stress incontinence	9 (5%)	-
Bulking material injected into bladder	7 (4%)	-
Fatigue	3 (2%)	2 (3%)
Abnormal urinalysis	3 (2%)	-
Bladder fullness	3 (2%)	-
Nocturia	3 (2%)	1 (1%)
Pelvic heaviness	3 (2%)	1 (1%)
Uterine fibroids	3 (2%)	-
Fever	2 (1%)	2 (3%)
Feeling of bladder not emptying	1 (<1%)	2 (3%)
Other (<2%)	35 (N/A)*	12 (N/A)

* "Other" treatment related adverse events in URYX patients, occurring at frequencies of < 2%, were as follows (listed alphabetically): abdominal upset,

bladder spasms, bladder stones, body aches, burning pain, cold and shivering, cyst, cystitis, feeling of decreased sensation with urination, felt faint during bulking injection, garlic odor, genital pain, kidney stones, labia with erythema, lower back pain, medicinal smell to urine, nausea, partial urinary retention due to dementia, pyuria, removal of URYX, urethral burning sensation, urethral irritation, urethral redness, urethral soreness, urethral spasm, vaginal bleeding, and vulvar burning.

Most treatment related adverse events occurred within 24 hours of treatment and subsequently resolved within 30 days. At the time of database closure, 92% of treatment related adverse events were resolved. The following events were persistent or resolution was unconfirmed at the time of database closure (the number of events is shown in parentheses): urge incontinence (6); leakage of urine/stress incontinence (5); worsening of incontinence (onset of urge) (5); exposed material (4); uterine fibroids (3); urinary tract infection (2); urinary frequency (2); urinary urgency (2) and one event each of genitourinary (infection/tenderness), kidney stones, nocturia, pelvic pain, urethral redness, and URYX removal.

With one exception, the rates of adverse events observed in the URYX and control groups are similar to one another. The one notable difference in the frequency of treatment related adverse events between URYX and control groups is the occurrence of exposed bulking material, which was only reported among URYX-treated subjects (n=28, 16%). Exposed material was documented following treatment on cystoscopy (typically during retreatment). This event was often associated with other events, particularly delayed voiding, dysuria, urinary tract infection, hematuria, urinary frequency, and urinary urgency. However, the occurrence of exposed material did not impact the effectiveness endpoints. In all but two cases, exposed material events either healed spontaneously or resolved following removal of excess material during cystoscopic examination. For the two cases in which resolution was not documented, one patient continued to have exposed material at the 12-month exam, and the other patient was lost to follow-up.

The incidence of exposed material was different in the feasibility and expanded phases of the study. During the feasibility phase, exposed material was observed in 32% (9/28) of URYX subjects. Review of these cases by the applicant and investigators concluded that these events were due to inappropriate injection technique, particularly shallow placement and injection too proximal to the bladder neck. Therefore, the URYX instructions for use, which previously recommended a similar injection technique as other bulking agents, were revised for the expansion phase (summarized above under "Patient Assessments"). Implementation of the modified URYX injection instructions reduced, but did not eliminate, the incidence of exposed material (i.e., 13%, 19/146).

Other observations regarding the adverse event data are as follows:

- Severity: Each adverse event was rated as "mild," "moderate," or "severe," with "severe" events defined as causing marked limitation in usual activities, requiring medical intervention or hospitalization. Similar proportions of patients in each study arm experienced genitourinary adverse events rated as "mild" and "moderate." However, 10 (6%) URYX subjects experienced a total of 14 "severe" genitourinary events, as compared to none in the control arm. These events consisted of: exposed material (n=3); bulking material injected in bladder (n=2); delayed voiding (n=2); urge incontinence (n=2); bladder spasms (n=1); bladder

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stones (n=1); hematuria (n=1); pelvic pain (n=1); and urinary frequency (n=1). These three cases of exposed material were classified as "severe" due to the use of cystoscopy to remove URYX material from the bladder or urethra. Except for one case of urge incontinence, all severe treatment related events were documented to have resolved.

- Onset: Nearly all adverse events in both groups occurred within 90 days after treatment. However, the adverse event rate experienced by URYX subjects was notably higher than that in the control arm during the following time intervals: (i) Days 2-30 (27% URYX, 9% control); and (ii) Days 31-90 (21% URYX, 6% control). These differences are likely explained by the occurrences of exposed material in the URYX arm, which were documented on repeat cystoscopy (typically performed > 30 days following treatment). After 90 days, few patients in either arm reported adverse events.
- Resolution: Analysis of the time to resolution of adverse events demonstrates that the majority of adverse events in both groups resolved within 30 days of onset. However, the proportions of patients experiencing adverse events lasting (i) 15-30 days (32% URYX, 6% control) and (ii) > 30 days (44% URYX, 22% control) were both higher in the URYX group. This difference in adverse events of longer duration relates to the occurrence of exposed bulking material in the URYX group. By the date of database closure, 92% of adverse events reported in the URYX group had resolved (similar to that reported for the control group).
- Retreatment: There is a trend (not statistically significant) of increased incidence of complications with increased number of treatments (particularly with urinary urgency, delayed voiding, UTI, and pelvic pain), and this trend is consistent between URYX and control groups.
- Route of Administration: URYX patients treated by the periurethral route had a significantly higher overall incidence of genitourinary adverse events than those treated by the transurethral route (88% versus 68%, respectively; $p=0.0305$). Also, URYX patients treated via periurethral injection reported a higher rate of urge incontinence (31% vs. 4%; $p<0.001$). Although similar trends were observed in the control group, the differences were not statistically significant. Based on these findings, the URYX instructions for use are limited to transurethral administration.
- Study Phase: For the URYX group, the overall incidence of genitourinary adverse events was lower in the expanded study phase (i.e., 68%) than in the feasibility phase (93%). This same observation was true for the following specific event categories: dysuria, urinary urgency, urinary frequency, and hematuria. These findings suggest that modified URYX instructions for use, combined with investigator training and experience with this device, were effective in improving the safety profile of URYX.

Cystoscopic examinations were performed at 1 month following final treatment in all U.S. feasibility patients, using a mucosal grading system to rate the appearance of the treatment site. These examinations were rated as "abnormal" in 50% (5/10) of URYX patients, as compared with 20% (1/5) control patients. During the expanded phase, interim cystoscopic exams were performed either at retreatment or other times at the investigator's discretion. These interim cystoscopic findings identified abnormal results in 30 subjects (27 URYX, 3 control). These abnormal findings were typically either exposed material or minor observations (e.g., residual material tags at the injection site, urethral redness), and were not regarded as clinically significant.

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 URYX is safe for long-term implantation in the urethral submucosa, and justify a 36-month shelf life.

The clinical data demonstrate that URYX treatment has a reasonable assurance of safety and effectiveness. In an intent to treat analysis of URYX subjects (using LOCF to impute missing data), improvement in continence was achieved at 12 months in approximately half of patients. Using this same dataset, dryness was achieved in 18.4% of URYX patients when defined as Stamey Grade = 0, and 37.8% when defined as pad weight ≤ 2 grams. URYX patients reported an increase in mean quality of life score (IQOL) 12 months after treatment, with 22% experiencing an increase of ≥ 50%. These results are equivalent to those of the control population.

With the exception of exposed material, the rates and severity of adverse events observed in the URYX and control groups are similar to one another. Although exposed material was not observed in the control group, its incidence was reduced during the course of the trial following modifications to the URYX injection procedure. Additionally, cases of exposed material were not associated with serious sequelae and resolved spontaneously in nearly all instances. Overall, adverse events associated with the use of URYX were generally transient and minor. There were no reports of serious unanticipated adverse device events or patient deaths. Due to the increased incidence of genitourinary adverse events among patients treated periurethrally, the administration of URYX treatment is limited to transurethral injection. Given this information, along with the fact that URYX is not associated with sensitization/anaphylactic reactions, is not prone to enzymatic degradation, and is easy to inject through a small gauge needle, it can be concluded that the benefits of URYX outweigh any increased risks when injected using the specific technique described in the labeling (i.e., transurethral injection, ≥ 2 cm from the bladder neck, needle angle = 30-45°, ≤ 1.0 mL/site and 2.5 mL/treatment, rate = 1 mL/min, and maintain needle at site for ≥ 1 minute after the injection). A key factor in this conclusion is the requirement that physicians complete a training program on URYX treatment.

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 URYX is safe and effective when used in accordance with the directions for use. Therefore, the PMA is approved, subject to the requirements that:

- Genyx create and administer a physician training program on the specific injection technique needed for the use of URYX;
- Genyx perform a 5-year postapproval study to (i) assess the long-term safety and effectiveness of URYX (e.g., durability of the treatment effect, the impact of retreatment); and (ii) confirm that the incidence of material exposure has been minimized with the modifications to the instructions for use.
- Genyx conduct a 2-year enhanced surveillance program, in which U.S. physicians using URYX will be contacted on a quarterly basis to actively solicit information on adverse events.

In Amendment 6, received by FDA on December 14, 2004, Genyx submitted these training and postapproval study plans.

FDA issued an approval order on December 16, 2004.

The applicant's manufacturing facility was inspected on April 29, 2003, and was 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, Contraindications, 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. "Draft Guidance for Preclinical and Clinical Investigations of Urethral Bulking Agents Used in the Treatment of Urinary Incontinence," FDA, CDRH, November 29, 1995 (http://www.fda.gov/cdrh/ode/oderp850.html).

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