SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Urethral Bulking Agent

Device Trade Name: Bulkamid® Urethral Bulking System

Device Procode: LNM

Applicant's Name and Address: Contura International A/S
Sydmarken 23
2860 Soeborg, Denmark

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P170023

Date of FDA Notice of Approval: January 28, 2020

II. INDICATIONS FOR USE

Bulkamid Urethral Bulking System is indicated for urethral injection for the treatment of stress urinary incontinence (SUI) due to intrinsic sphincter deficiency (ISD) in adult women who have SUI or stress predominant mixed incontinence.

III. CONTRAINDICATIONS

Bulkamid Urethral Bulking System must not be used in patients suffering from acute urinary tract infection.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Bulkamid Urethral Bulking System labeling.

V. DEVICE DESCRIPTION

Bulkamid Urethral Bulking System (i.e., "Bulkamid") is a permanently implanted, non-resorbable, injectable, transparent, hydrogel for urethral bulking. Bulkamid hydrogel consists of cross-linked polyacrylamide (2.5% w/w) and water (97.5% w/w), which is supplied sterile in 1 mL pre-filled syringes.

The Bulkamid Urethral Bulking System is a single-use kit comprised of the following components:

- 2 syringes containing 1 mL Bulkamid hydrogel (steam sterilized),

- 1 Bulkamid Rotatable Sheath (7.3 mm diameter, 50 mm working length, ethylene oxide sterilized), and
- 2 Bulkamid injection needles (23 gauge, 12 cm length, ethylene oxide sterilized).

A commercially available, reusable cystoscope (2.7 x 113 mm, 0º) is provided separately.

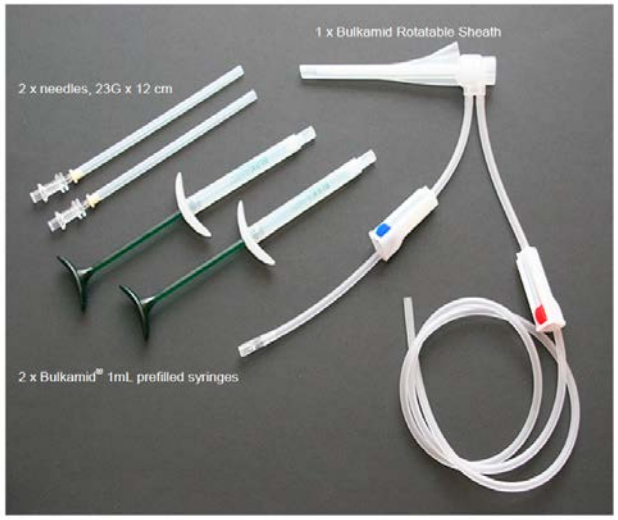


Figure 1. Bulkamid Urethral Bulking System components

Figure 2. Bulkamid Urethral Bulking System components assembled for use, with cystoscope

Bulkamid is injected under cystoscopic visualization into the urethral submucosa distal to the bladder neck until urethral coaptation is achieved. Refer to the Bulkamid Urethral Bulking System labeling for additional details.

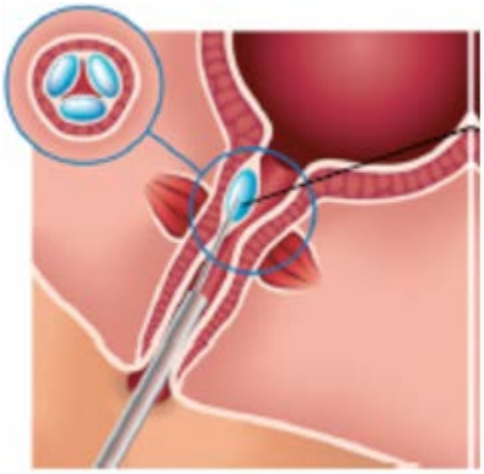


Figure 3. Depiction of the injection of Bulkamid into the urethral submucosa

Following injection into the tissue, Bulkamid replaces the extracellular matrix and allows in-growth of host cells and vessels. Bulkamid creates increased tissue bulk, resulting in reduced urinary incontinence.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of female stress urinary incontinence.

- 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.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Bulkamid is currently marketed in over 20 countries, including Europe, Canada, South Africa, and Australia. Bulkamid 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

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Acute retention
- De novo urge incontinence
- Dysuria
- Embolic phenomena
- Erythema
- Excreted material
- Granuloma
- Hematuria
- Incomplete bladder emptying/outlet obstruction
- Migration of injected material
- Pain at implant site
- Urethral erosion

- Urinary tract infection (UTI)
- Urinary frequency
- Urinary urgency
- Vaginal infection/irritation
- Vascular occlusion
- Worsening urinary incontinence

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Table 1 shows the hydrogel characterization testing performed on Bulkamid. The device met all established acceptance criteria:

Table 1. Hydrogel Characterization Testing

Test	Acceptance Criteria	Results
Osmolality (tonicity)	N/A (characterization purposes only)	9.4 mosmol/L
Swelling (semi-confined)	N/A (characterization purposes only)	293 Pa
Particle size distribution (light scattering)	N/A (characterization purposes only)	Mean = 585 µm Range = 332-1007 µm
IR spectrum	Manufacturer's pre-specified reference spectrum	Complies with reference spectrum
Refractive index	1.3333-1.3410	1.3364-1.3369
Appearance (visual)	Transparent, viscous gel	All samples met specifications for visual appearance
Residual acrylamide monomer	≤ 1.5 ppm	0.3 ppm
Residual N,N-methylene-bis-acrylamide monomer	≤ 1 ppm	< 0.1 ppm
Impurities	< 5 ppm	< 5 ppm
pH	7.0-9.0	8.15-8.22
Elasticity modulus	55-90 Pa	59.0-76.5 Pa
Loss on drying	97.5 ± 0.3%	97.6%
Dry matter	2.5 ± 0.3%	2.4%

Table 2 shows the syringe performance verification testing performed on Bulkamid. The device met all established acceptance criteria:

Table 2. Syringe Performance Verification Testing

Test	Acceptance Criteria	Results
Leakage from fitting assembly	No leakage under 300-330 kPa pressure (per ISO 80369-7)	No sample leaked
Unscrewing torque of tip cap	< 240 N-mm (per ISO 80369-7 and 20)	95.9-173.6 N-mm
Injection force	< 70 N (per ISO 11608-3)	Initiation force: 46.3-64.5 N Sustaining force: 38.2-54.6 N
Fill volume accuracy	≥ 1.0 mL (per manufacturer's specifications)	All syringes contained ≥ 1.0 mL hydrogel
Syringe/needle compatibility (i.e., luer gaging test)	Cone insertion depth tolerance < 1.7 mm (per ISO 594-1)	All luers conformed within the specified tolerance

B. **Animal Studies**

Animal studies were conducted to assess the safety of Bulkamid hydrogel when implanted *in vivo*. The testing demonstrated that the system met the safety endpoints. All animal studies were conducted in compliance with Good Laboratory Practices (GLPs), 21 CFR Part 58. Key information from the animal studies is summarized in Table 3 below.

Table 3. *in vivo* Animal Studies

Test	Test Objective	Results/Conclusion
2-year implantation study in female sheep	To evaluate the local and systemic effects following short- and long-term exposure to Bulkamid hydrogel when injected into urethral submucosal tissue.	There were no significant differences between treatment and control animals with regard to organ weights or blood/urine chemistries. There were no significant unexpected device-related adverse events. Gross pathology documented that Bulkamid was palpable at the implant site in the majority of sheep at all time points. Minimal acute inflammation related to the subject device was present by Day 8. A minimal/mild foreign body reaction was present by Day 30, which persisted at all subsequent time points in the study (3, 6, 12, and 24 months). There was no migration of the subject device.

Test	Test Objective	Results/Conclusion
Sub-chronic (13-week) testicular and ovary/uterine toxicity (implant method) test in rabbits	To evaluate the effects of Bulkamid exposure (intra-muscular injection) on the testes and ovaries/uteri	There were no significant differences between test and control animals with regard to gross and microscopic observations of female reproductive organs. In male test and control animals, the gross and microscopic testicular observations were interpreted to be normal incidental findings of New Zealand White Rabbits, with the exception of severe testicular atrophy observed in a single test animal. The relationship between this testicular finding and Bulkamid has not been definitively established. However, this is not considered to be a significant toxicologal concern given that the labeling restricts use of the device to women.

C. **Biocompatibility**

Biocompatibility testing was performed for all patient-contacting components of the Bulkamid Urethral Bulking System in accordance with ISO 10993-1 *Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process*, on the finished sterilized devices. All biocompatibility studies were conducted in compliance with GLPs, 21 CFR Part 58.

Bulkamid hydrogel is considered to be a permanent (> 30 days) implant in contact with tissue. The following biocompatibility endpoints were assessed for this device component (samples obtained from pre-filled syringes):

- Cytotoxicity
- Irritation/Intracutaneous Reactivity
- Sensitization
- Genotoxicity
- Material-Mediated Pyrogencity
- Hemocompatibility (syringe component only)
- Implantation (13 weeks)
- Toxicological Risk Assessment of compounds extracted from the device to evaluate chronic systemic toxicity, reproductive toxicity, and carcinogenicity

The Bulkamid Rotatable Sheath is considered to be a surface device, in contact with mucosal membrane for limited duration (≤ 24 hrs.). The following biocompatibility endpoints were assessed for this device component:

- Cytotoxicity
- Irritation/Intracutaneous Reactivity
- Sensitization

The Bulkamid Needle is considered to be an externally communicating device, in contact with the blood path (indirect, non-circulatory) for limited duration (≤ 24 hrs.). The following biocompatibility endpoints were assessed for this device component:

- Cytotoxicity
- Irritation/Intracutaneous Reactivity
- Sensitization
- Acute Systemic Toxicity
- Material-Mediated Pyrogenicity
- Hemolysis

All pre-specified test acceptance criteria were met and all tests passed. In the implantation study for the Bulkamid hydrogel, testicular anomlies were observed in some male rabbits implanted with Bulkamid. The relationship between these anomalies and Bulkamid have not been definitively established. There were no findings in the female rabbits implanted Bulkamid. Based on these observations, the patient and physician labeling specify a warning that Bulkamid should not be used in male subjects.

D. **Sterility**

The Bulkamid components that are provided sterile are terminally sterilized using either (i) a steam sterilization cycle (for the Bulkamid syringe pre-filled with hydrogel) or (ii) an ethylene oxide (EO) sterilization cycle (for the Bulkamid Rotatable Sheath and Needle). Validation of the sterilization processes demonstrate a Sterility Assurance Level (SAL) of 10^{-6} and are in compliance with *ANSI/AAMI/ISO 17665-1:2006 Sterilization of health care products - Moist heat - Part 1: Requirements for the development, validation, and routine control of a sterilization process for medical devices*, and *ANSI/AAMI/ISO 11135-1:2014 Sterilization of health care products - Ethylene oxide - Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices*. For the EO sterilized components, sterilant residuals conform to the maximum allowable limits of EO and Ethylene Chlorohydrin (ECH) residuals specified in *ISO 10993-7:2008 Biological Evaluation of Medical Devices - Part 7: Ethylene Oxide Sterilization Residuals*. The product bacterial endotoxin limits were chosen based on FDA's *Guidance for Industry - Pyrogen and Endotoxins Testing: Questions and Answers* (June 2012) and were verified using Limulus Amebocyte Lysate (LAL) testing. Routine LAL batch release testing is performed.

E. **Packaging and Shelf-Life**

The system is supplied in a box containing the following components, each in sterile barrier packaging:

- 2 syringes pre-filled with hydrogel (packaged in a tray with Tyvek lid),
- 1 Bulkamid Rotatable Sheath (packaged in a Tyvek pouch), and
- 2 Bulkamid Needles (in paper pouches)

Package integrity testing was successfully completed to verify that the packaging materials were able to withstand the rigors of shipping and distribution.

Real time shelf-life testing was conducted on the Bulkamid components (i.e., repeat of hydrogel characterization and syringe performance studies) and packaging to support a labeled shelf-life of 3 years.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of urethral bulking with Bulkamid for the treatment of female SUI due to ISD in the US and Canada under IDE number G070144. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between June 4, 2008 and July 29, 2011. The database for this PMA reflected data collected through August 31, 2012 and included 345 patients. There were 33 investigational sites (28 US, 5 Canada).

The study was a prospective, two-arm, single-blinded, randomized clinical study. The objectives of the study were to assess the safety and effectiveness of Bulkamid in the treatment of female with SUI due to ISD, and to demonstrate non-inferiority to an active control consisting of a legally marketed alternative with similar indications for use (i.e., the Allergan Inc. Contigen Bard Collagen Implant). If the primary effectiveness endpoint analysis supported the conclusion that Bulkamid is non-inferior to control, the results were to be tested for superiority.

Enrolled patients were randomized 2:1 between Bulkamid and control, stratified using permuted block randomization.

The study hypothesis was that the proportion of Bulkamid subjects achieving success in the primary effectiveness endpoint at 12 months following last injection is no worse than that observed in the control arm minus a non-inferiority margin (δ). Using the Blackwelder method, a minimum required sample size of 354 patients was calculated (236 Bulkamid, 118 control) based on the following assumptions:

P1 = P2 = 0.65 (expected success rate for Bulkamid and control)
α (one-sided type I error) = 0.05
β (type II error) = 0.20
δ (non-inferiority margin) = 0.15
Drop-out rate = 20%
Pooled z-test (normal approximation to the binomial)

The protocol specified that the primary safety and effectiveness analyses of Bulkamid were to be assessed using the intent-to-treat (ITT) approach, where missing effectiveness data were imputed using last observation carried forward (LOCF). Additionally, sensitivity analyses, including multiple imputation and tipping point analysis, were performed to assess the potential impact of missing effectiveness data on the study conclusions.

Logistic regression was used to explore the impact of several covariates on the primary effectiveness endpoint, including age, baseline pad weight, number of incontinence episodes, duration of incontinence, number of pregnancies, and center.

No interim analysis was planned. No hypothesis tests were specified for the secondary endpoints.

An independent physician not participating in the clinical study served as medical monitor and performed the following functions: (i) provided medical and scientific input in the review of the clinical data, subject medical safety data, and laboratory values; (ii) maintained ongoing assessment of the Bulkamid safety profile; and (iii) provided medical surveillance and evaluation of serious adverse events (SAEs).

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the study was limited to patients who met the following inclusion criteria:

   - Female, ≥ 18 years of age.
   - Patients of childbearing potential or < 2 years' post-menopausal must have been using two forms of contraception, (i.e., intrauterine device, oral contraceptive for at least one cycle, implant or double barrier spermicide method) and have a negative urine or serum pregnancy test at screening/baseline. Complete abstinence may have been considered acceptable, but must first be discussed on a case-by-case basis with the study clinician or project manager.
   - Diagnosis of SUI due to ISD, or stress predominant mixed incontinence, for at least 6 months.
   - Failed two previous non-invasive therapies for 3 months each (e.g., behavioral modification, electrical stimulation, pelvic muscle exercise, biofeedback, and/or drug therapy).

- Documentation of at least 3 incontinence episodes measured over 3 days.
- Baseline 24-hr. pad weight test ≥ 5 g.
- Valsalva leak point pressure (VLPP) ≤ 100 cm H_2O.
- Maximum cystometric capacity ≥ 250 mL.
- Maximum detrusor pressure < 25 cm H_2O during filling cystometry.
- Post void residual (PVR) urine ≤ 100 mL.
- Clinical laboratory values within normal limits, or if abnormal, considered and documented as not clinically significant by the investigator.
- Life expectancy of more than 2 years.
- Been informed of, and be able to perform, the study treatments and procedures, and signed an informed consent form.
- Provided authorization to use and disclose information for research purposes [HIPAA (Health Insurance Portability and Accountability Act of 1996; US sites) or country-specific requirement].

Patients were <u>not</u> permitted to enroll in the study if they met any of the following exclusion criteria:

- Urethral hypermobility with a straining angle > 30º from horizontal bladder neck.
- Predominant urge incontinence.
- Detrusor overactivity.
- Regularly or intermittently used a urethral catheter.
- Previous radiation treatment in the pelvic floor.
- Previous urethral surgery (i.e., fistula or diverticula) or previous urethral bulking. Subjects who have residual or recurrent SUI following a colposuspension or a sling procedure may be included in the study if the procedure was conducted at least 6 months prior to the screening/baseline visit.
- Polyuria (≥ 3 L/24 hrs.).
- Three or more culture-proven bacterial UTIs in the last 12 months.
- Current infection (urethritis, cystitis or vaginitis).
- Unevaluated hematuria.

- Prolapse greater than Stage II using the ICS Pelvic Organ Prolapse Quantification (POPQ) exam.
- Body mass index (BMI) > 35 kg/m^2.
- Currently taking, or has taken within 4 weeks prior to the screening/baseline visit, pharmacological treatment for SUI (including but not limited to, alpha adrenergics, and tricyclic antidepressants).
- Allergy to bovine collagen.
- History of severe allergies or anaphylaxis including hypersensitivity to local anesthetics such as lidocaine, antibiotics used for treating urinary tract infections or dietary beef allergy.
- Was having or was planning desensitization injections to meat products.
- Autoimmune diseases (e.g., connective tissue diseases) that could affect or confound treatment outcome.
- Classification by the American Society of Anesthesiologists' physical status classification > 2.
- Currently taking, or has taken, within 3 months prior to the initial treatment visit, systemic corticosteroids.
- Currently has cancer or has a history of cancer within the past 5 years. Subjects with a history of skin cancer with no evidence of skin malignancy for 2 years can be included. Note: basal cell carcinoma was not an exclusion criterion.
- Any unstable or severe cardio-vascular disease.
- Uncontrolled diabetes.
- Active herpes genitalis.
- Currently participating in any other clinical trial, or has participated in another clinical trial within 3 months prior to the screening/baseline visit.
- History of drug/alcohol abuse, mental dysfunction, or other factors limiting her ability to cooperate fully.
- Pregnant, lactating, or not practicing adequate contraception (refer to inclusion criteria), was intending to become pregnant, or to lactate for the duration of this study (approximately 12 months).
- Not physically able to perform study procedures.
- Neurogenic bladder.

- Vaginal delivery within 3 months prior to the screening/baseline visit.
- Any other condition, which, in the opinion of the investigator, would have made the subject not a suitable candidate for the study.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations 1 month after the initial and any subsequent injections, and at 3, 6, and 12 months following the final injection. Additionally, all patients received telephone follow-up 9 months following the final injection. The study permitted Bulkamid and control patients to receive a maximum of 3 injections (initial injection plus 2 re-injections). Patients who were incontinent at the 1 month exam were eligible for re-injection of the assigned randomized treatment. To be eligible for re-injection, a patient was considered incontinent if she reported any stress incontinence episodes in the voiding diary or reported stress incontinence on self-assessment questions.

Pre-injection, patients underwent a physical examination and medical history, Q-tip test, urinalysis and blood tests (including pregnancy test, if necessary), cystometry, VLPP, PVR, voiding volume, 24-hr. pad weight test, 3-day voiding diary, and questionnaires (Urinary Incontinence Quality of Life Scale (IQoL), International Consultation on Incontinence Modular Questionnaire – Urinary Incontinence (ICIQ-UI) Short Form, and Pelvic Organ Prolapse – Urinary Incontinence Sexual Function Questionnaire (PISQ)). Post-injection, the objective parameters measured during the study included the 24-hr. pad weight test and 3-day voiding diary. Adverse events and complications were recorded at all visits.

The key timepoints are shown in Table 4 and in the tables summarizing safety and effectiveness.

Table 4. Post-Injection Schedule of Events

24-hr. pad weight test	1 month following each injection, and 3, 6, and 12 months following final injection
3-day voiding diary	1 month following each injection, and 3, 6, and 12 months following final injection
IQoL & ICIQ-UI Short Form	3, 6, and 12 months following final injection
PISQ	6, and 12 months following final injection
Subject perception of incontinence	3, 6, 9, and 12 months following final injection
Subject self-assessment of incontinence	1 month following each injection, and 3, 6, 9, and 12 months following final injection

Concomitant medication assessment	1 month following each injection, and 3, 6, and 12 months following final injection

3. Clinical Endpoints

With regards to safety, the primary endpoint was the incidence of device- and procedure-related serious adverse events (SAEs) through the 12-month follow-up visit. Secondary endpoints were:

- Incidence and severity of all procedure- and device-related adverse events through the 12-month follow-up visit.
- Incidence of all adverse events through the 12-month follow-up visit.

With regards to effectiveness, the primary endpoint was reduction from baseline in both urine leakage (as measured by a 24-hr. pad weight test) and daily number of incontinence episodes (as documented in a voiding diary) at the 12-month follow-up visit. Secondary endpoints, all assessed at the 12-month follow-up visit, were:

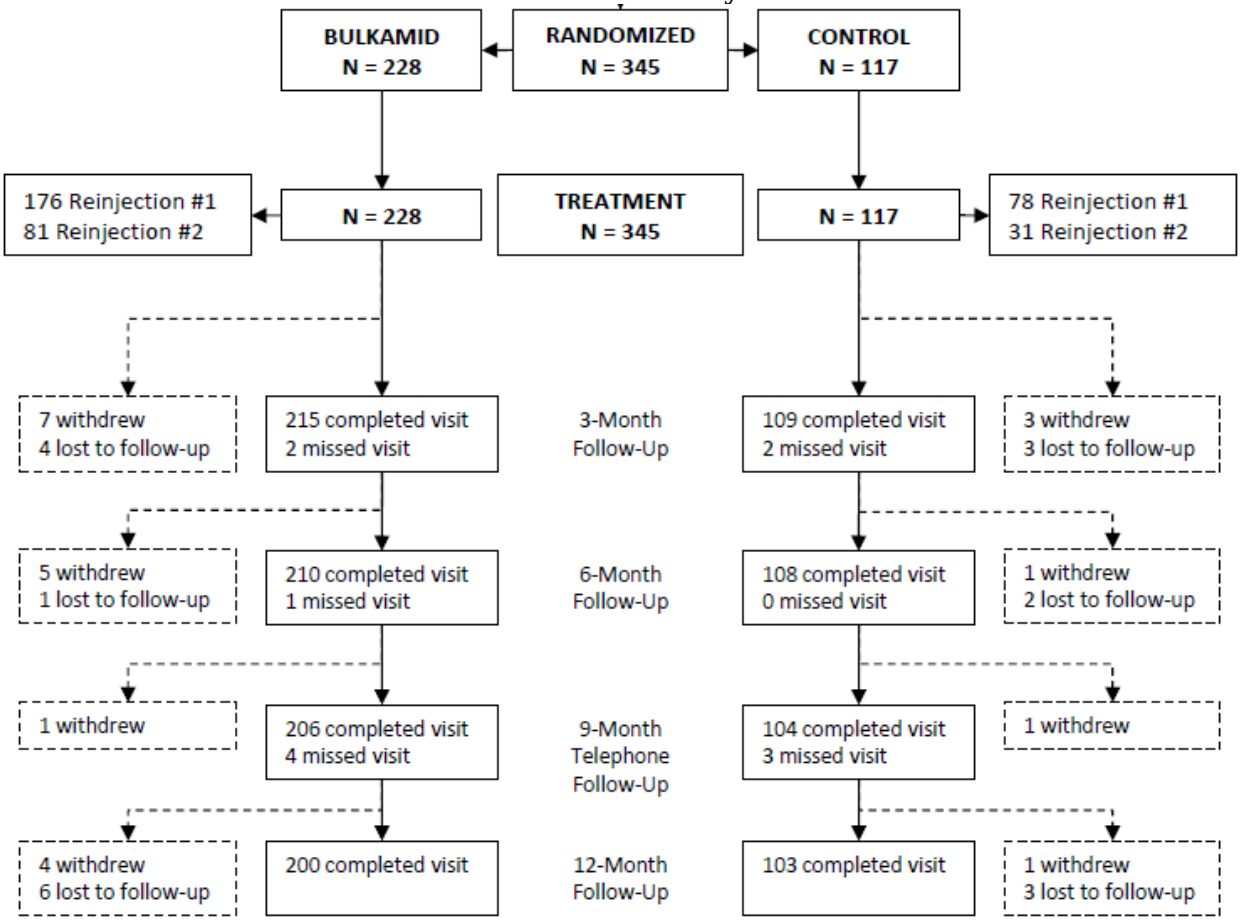
- Proportion of subjects dry according to the 24-hr. pad test (i.e., $\leq$ 4g leakage).
- Change from baseline in the 24-hr. pad test.
- Proportion of subjects dry according to the ICIQ-UI questionnaire.
- Change from baseline in the average daily number of incontinence episodes (stress, urge, and all urinary incontinence episodes) based on voiding diary.
- Proportion of subjects with no SUI episodes based on voiding diary.
- Responder rate ("improved," "much improved" or "cured/dry") based on the subject perception of effectiveness.
- Change from baseline in IQoL score.
- Change from baseline in ICIQ-UI score.

With regard to success/failure criteria, a patient was considered to be a "success" if she achieved at least a 50% reduction from baseline in both urine leakage (as measured by a 24-hr. pad weight test) and daily number of incontinence episodes (as documented in a voiding diary) at the 12-month follow-up visit. The study was considered to be a success if Bulkamid was determined to be non-inferior to control with respect to the proportion of patients achieving this success criterion.

B. **Accountability of PMA Cohort**

At the time of database lock, of 345 patients (228 Bulkamid, 117 control) enrolled in the PMA study, 87.8% (303) patients were available for analysis at the completion of the 12-month follow-up visit. The percent of patients remaining in the study through the 12-month follow-up visit was similar for Bulkamid (87.7%) and control (88.0%).

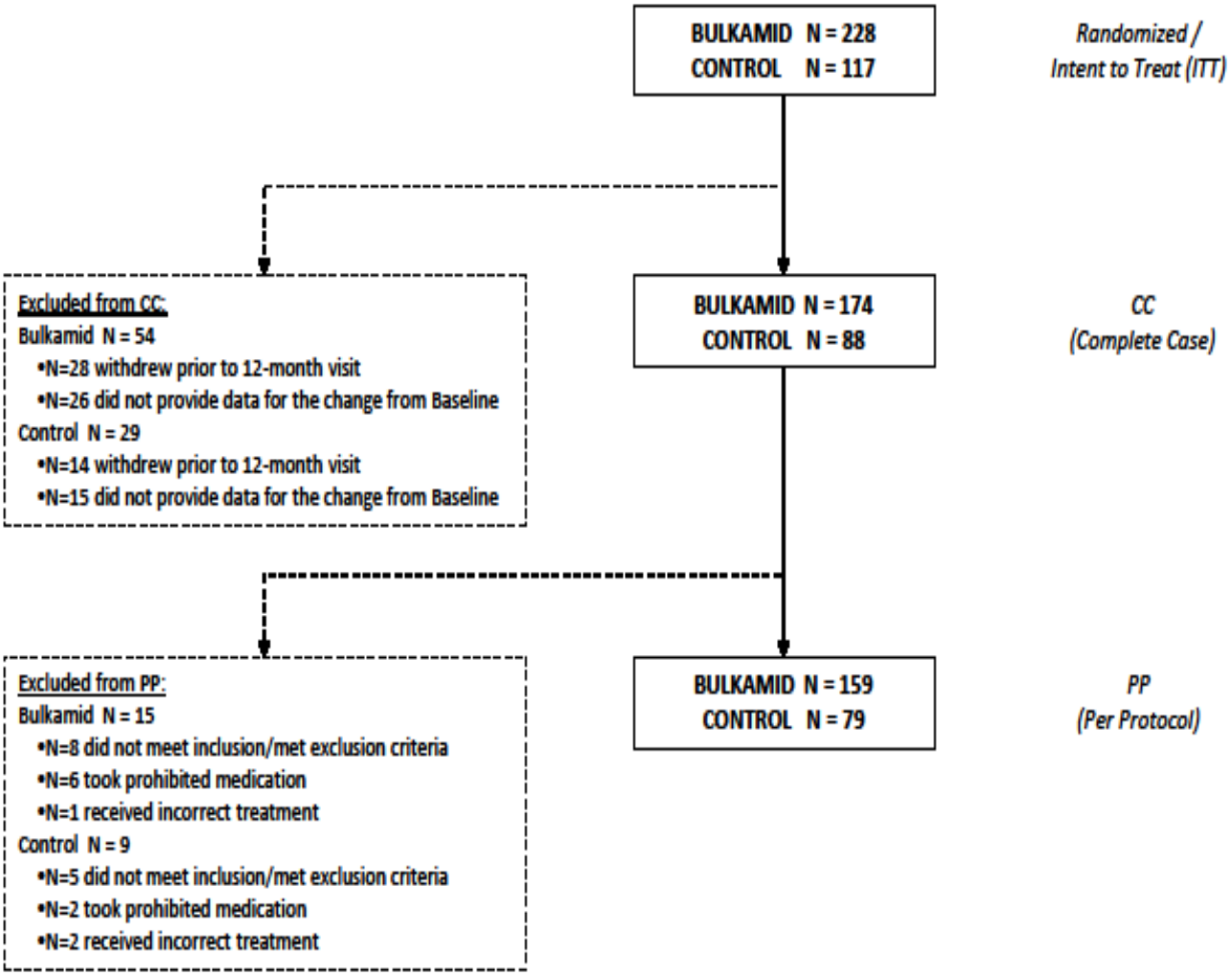
Patient Accountability Tree



The protocol defined the following analysis sets for the analysis of the study endpoints:

- Intent-to-Treat (ITT) (228 Bulkamid, 117 control): All randomized subjects enrolled in the study. The data were to be analyzed according to the randomization assignment, and not how the subject was ultimately treated. The primary safety and effectiveness endpoint analyses were based on the ITT analysis set. For the primary effectiveness endpoint analysis, missing values were to be imputed at 12 months using the LOCF method.
- Completed Case (CC) (174 Bulkamid, 88 control): Randomized subjects with complete data for a specific endpoint at a particular time point (no imputed data). This analysis set was used for the secondary effectiveness endpoint analyses.
- Per-Protocol (PP) (159 Bulkamid, 79 control): Subjects with complete data for the primary effectiveness endpoint and no major protocol deviations (i.e., enrolled consistent with all inclusion/exclusion criteria, did not take a prohibited concomitant medication, and were treated in accordance with the randomization assignment). This analysis set was used for the secondary effectiveness endpoint analyses.

The patient accountability for each analysis set is summarized below:



C. **Study Population Demographics and Baseline Parameters**

The demographics of the study population are typical for an injectable urethral bulking agent study performed in the US. Patients were adult females, ranging in age from 23 to 93 years. Table 5 displays the demographics and baseline characteristics of the study population.

Table 5. Demographics and Baseline Characteristics

Characteristic	**Bulkamid** (n=228)	**Control** (n=117)
Age (yrs.)		
Mean	58.0	57.4
Median	58.4	56.8
Range	23.3, 93.4	29.5, 85.4

Characteristic	**Bulkamid** (n=228)	**Control** (n=117)
Ethnicity		
Hispanic or Latina	9.6%	9.4%
Not Hispanic or Latina	90.4%	90.6%
Race		
White	93.9%	93.2%
Asian	1.8%	2.6%
Black or African American	0.9%	0.9%
American Indian or Alaska Native	0.9%	0.9%
Native Hawaiian or Other Pacific Islander	0.0%	0.0%
Other	2.6%	2.6%
Weight (kg)		
Mean	74.3	71.9
Median	72.6	71.2
Range	43.5, 106.6	48.1, 103.4
BMI (kg/m^2)		
Mean	27.9	27.0
Median	27.6	26.9
Range	17.0, 44.5	18.7, 34.8
Baseline Clinical Conditions (%)		
Head, eyes, ears, nose, throat	0.0%	0.0%
Cardiovascular	0.0%	0.0%
Pulmonary	0.0%	0.0%
Neurological	0.0%	0.0%
Gastrointestinal	0.0%	0.0%
Musculoskeletal	0.0%	0.0%
Urogenital (other than SUI)	0.4%	0.9%
Integumentary	0.0%	0.0%
Duration of SUI (yrs.)		
Mean	9.5	8.9
Pad weight (g)		
Mean	93.6	115.4
IQoL score		
Mean	49.5	47.3
Type of urinary continence (%)		
Stress	13.2%	11.1%
Mixed stress/urge	82.0%	83.8%
Number of pregnancies (%)		
None	8.8%	9.4%
1-2	43.4%	41.9%
3-4	36.0%	32.5%
>4	11.8%	16.2%
Prolapse stage (%)		
0	71.4%	71.6%
I	16.7%	16.4%

Characteristic	Bulkamid (n=228)	Control (n=117)
II	11.9%	12.1%
III or IV	0.0%	0.0%
Prior failed non-invasive therapies (%)		
Behavioral modification	85.5%	81.2%
Electrical stimulation	2.2%	2.6%
Pelvic muscle exercise	97.8%	95.7%
Drug therapy	21.9%	26.5%
Biofeedback	2.6%	6.8%
Other	15.9%	13.7%
Prior failed invasive therapies (%)		
None	75.0%	74.4%
Bulking (*protocol deviation*)	0.9%	0.0%
Sling	18.4%	22.2%
Other incontinence surgery	9.2%	6.8%
Other pelvic surgery	8.3%	6.8%

The demographics of the study population are consistent with the general female SUI population with respect to age. While the racial and ethnic backgrounds of study subjects are predominantly white and non-hispanic/non-latina, this is similar to other studies of injectable urethral bulking agents and is unlikely to impact the study conclusions.

The Bulkamid and control groups are closely matched regarding demographics and baseline clinical history, including incontinence status.

Table 6 summarizes the number of injections received per patient for the ITT population, and the volume injected per patient. The protocol permitted patients to receive up to 3 injections (initial injection plus 2 re-injections), based on the patient's continence status at the 1-month follow-up visit. The number of injections administered was similar for the two treatment groups. However, due to differences in the material compositions and directions for use for Bulkamid and control, the mean volume injected per patient was lower in the Bulkamid group.

Table 6. Injection Information

Parameter	Bulkamid (n=228)	Control (n=117)
Number of injections received:		
1	22.8%	33.3%
2	41.7%	40.2%
3	35.5%	26.5%
Mean volume of initial injection (mL)	1.6	4.7
Mean volume of first re-injection (mL)	1.5	4.1
Mean volume of second re-injection (mL)	1.6	4.4
Mean total volume of all injections (mL)	3.3	8.6

D. **Safety and Effectiveness Results**

1. Safety Results

The analysis of safety was based on the ITT analysis set of 345 patients (228 Bulkamid, 117 control), evaluating all adverse effects observed through the 12-month evaluation. No deaths were reported in either the Bulkamid or control groups during the study period, and there were no serious unanticipated adverse device effects. Other key safety outcomes are presented below.

Adverse effects that occurred in the PMA clinical study:

The primary safety endpoint was the incidence of device- and procedure-related SAEs. The only such event that occurred in the study was a single procedure-related incidence of hematuria in a Bulkamid subject:

> Eight days after initial injection with Bulkamid, this subject who had recurrent idiopathic thrombocytopenia reported she could no longer urinate and discovered the presence of blood at the urethra. The subject was admitted to the hospital and found to be in urinary retention due to a blood clot. She was catheterized and received packed red blood cells. Her urinary retention and hematuria were resolved after 2 days, at which time she was discharged.

This single SAE is an anticipated event for injectable urethral bulking agents, and was readily resolved. From this analysis, Bulkamid and control are similar with respect to the primary safety endpoint.

The secondary safety endpoints were (i) the incidence and severity of all device- and procedure-related adverse events through the 12-month follow-up visit, and (ii) the incidence of all adverse events through the 12-month follow-up visit.

The device- and procedure-related adverse events through the 12-month follow-up visit are summarized in Table 7.

Table 7. Incidence of Device- and Procedure-Related Adverse Events

	Bulkamid (n=228)		**Control** (n=117)	
Adverse event type	**Events N**	**Subjects N (%)**	**Events N**	**Subjects N (%)**
Pain at implant site	39	28 (12.3%)	12	9 (7.7%)
Acute retention	14	13 (5.7%)	12	11 (9.4%)
UTI	10	8 (3.5%)	7	7 (6.0%)
Hematuria	3	3 (1.3%)	0	0 (0.0%)
De novo urge incontinence	2	2 (0.9%)	2	2 (1.7%)
Dysuria	2	2 (0.9%)	4	2 (1.7%)
Urinary urgency	2	2 (0.9%)	1	1 (0.9)

	Bulkamid (n=228)		Control (n=117)	
Adverse event type	**Events N**	**Subjects N (%)**	**Events N**	**Subjects N (%)**
Vaginal infection/irritation/ Lichen Sclerosus	1	1 (0.4%)	0	0 (0.0%)
Worsening urinary incontinence	1	1 (0.4%)	0	0 (0.0%)
Non-acute urinary retention (> 7 days)	0	0 (0.0%)	3	3 (2.6%)
Pelvic pain	0	0 (0.0%)	3	3 (2.6%)
Urinary frequency	0	0 (0.0%)	2	2 (1.7%)
Excreted bulking material	0	0 (0.0%)	1	1 (0.9%)
Nocturia	0	0 (0.0%)	1	1 (0.9%)
Outlet obstruction	0	0 (0.0%)	1	1 (0.9%)
"Other" event[1]	7	6 (2.6%)	1	1 (0.9%)
Total number of adverse events	81		50	
Number (%) of patients with at least 1 adverse event		60 (26.3%)		32 (27.4%)

[1]"Other" events observed in the Bulkamid group were: abnormal laboratory value (elevated total immunoglobulin E), back/neck pain, dizziness/fainting, extremity nerve pain/tingling, and inflammatory condition (gout).

Bulkamid and control patients had similar likelihoods of experiencing at least one device- or procedure-related adverse event (26.3% Bulkamid, 27.4% control). Additionally, the rates of each adverse event type had overlapping 95% confidence intervals. The three most common device-/procedure-related adverse events reported were the same for both groups: pain at implant site, acute retention, and UTI.

Across both Bulkamid and control patients, most device-/procedure-related adverse events resolved within 5 days (range = 0-88 days), and 93.8% of events were resolved at the time of study closure. For the Bulkamid group, the following 5 events were persistent or resolution was unconfirmed at the time of study closure: de novo urge incontinence (n=2), urinary urgency (n=2), and "other" inflammatory condition (n=1).

The severity of the device-/procedure-related adverse events was similar for Bulkamid and control. For the Bulkamid group, 64.2% of events were classified as mild, 33.3% were classified as moderate, and 2.5% were classified as severe. The severe events were: hematuria (n=1) and pain at implant site (n=1).

Analysis of all adverse events (reported independent of device-relatedness) yielded similar conclusions regarding the safety of Bulkamid.

2. Effectiveness Results

The primary analysis of effectiveness was based on the ITT analysis set of 345 patients (228 Bulkamid, 117 control), imputing missing data from the 12-month follow-up visit using the LOCF method. Secondary analyses of effectiveness were based on the CC and PP analysis sets. Key effectiveness outcomes are presented in Tables 8 to 10.

The primary effectiveness endpoint of the study was the proportion of subjects at the 12-month follow-up visit with at least a 50% reduction from baseline in both urine leakage (as measured by a 24-hr. pad weight test) and daily number of incontinence episodes (as documented in a voiding diary) at the 12-month follow-up visit. The results of this analysis are summarized in Table 8. The proportions of patients meeting this criterion for study success were 46.9% for Bulkamid, and 42.7% for control. This analysis demonstrated statistical significance for non-inferiority, but not for superiority.

Table 8. Primary Effectiveness Endpoint (ITT)

	Bulkamid	**Control**
N	228	117
N (%) successes (≥ 50% reduction)	107 (46.9%)	50 (42.7%)
P-value (non-inferiority, δ=15%)	0.0003	
P-value (superiority)	0.2286	

Sensitivity analyses of the primary effectiveness endpoint were conducted to test the influence of missing data on the robustness of the non-inferiority conclusion. These analyses are summarized in Table 9, and included the ITT analysis set using methods other than LOCF for imputing missing data, as well as the CC and PP analysis sets. Except for the extreme worst case of imputing all missing Bulkamid data as "failure" and all missing control data as "success," these analyses found Bulkamid to be non-inferior (NI) to control.

Table 9. Sensitivity Analyses of the Primary Effectiveness Endpoint

Analysis Set/Missing Data Handling Strategy[1]	**Bulkamid Success Rate**	**Control Success Rate**	**P-value (NI δ=15%)**
CC/No imputed data	51.7%	47.7%	0.0018
PP/No imputed data	52.8%	49.4%	0.0036
ITT/Missing data imputed with mean within treatment group	50.0%	47.9%	0.0013
ITT/All missing data imputed as failure	39.5%	35.9%	0.0004

Analysis Set/Missing Data Handling Strategy[1]	Bulkamid Success Rate	Control Success Rate	P-value (NI δ=15%)
ITT/All missing data imputed as success	61.8%	59.8%	0.0011
ITT/Best case (missing Bulkamid imputed as success, missing control imputed as failure)	61.8%	35.9%	<0.0001
ITT/Worst case (missing Bulkamid imputed as failure, missing control imputed as success)	39.5%	59.8%	0.8319
ITT/Multiple imputation[2]	50.9% (48.2%, 53.9%)	48.7% (44.4%, 52.6)	N/A
ITT/Multiple imputation (considering all early withdrawals as failure and imputing the remaining missing values)[2]	45.6% (44.1%, 47.8%)	42.7% (40.2%, 45.3)	N/A

[1]Subjects who withdrew from the study due to lack of effectiveness are considered failures in all sensitivity analyses.

[2]Results of multiple imputation are displayed as median success rates, along with the 2.5th and 97.5th percentiles.

In addition to the sensitivity analyses, tipping point analysis of the primary effectiveness endpoint was performed. Of the 1,566 combinations of possible missing data imputations, 77.7% resulted in the same non-inferiority conclusion.

To justify pooling of sites, a logistic regression model for the primary effectiveness endpoint was fit with three factors – site, treatment, and treatment-by-site interaction. The treatment-by-site interaction term had a p-value of 0.99, providing statistical evidence of the data being poolable across sites. For this analysis, sites with fewer than 10 randomized subjects were combined.

Table 10 summarizes the secondary effectiveness endpoint analyses. Each of these analyses are based on the 12-month follow-up results. Per the protocol, these analyses were performed for both the CC and PP analysis sets. Since similar conclusions were obtained for both analysis sets, only the CC results are summarized below.

Table 10. Secondary Effectiveness Endpoint Analyses (CC)

Secondary Effectiveness Endpoint[1]	Bulkamid	Control
Proportion of subjects dry according to the 24-hr. pad test (i.e., ≤ 4g leakage)	23.7%	24.5%
Change from baseline in the 24-hr. pad test[2]	-62.6g	-60.1g

Secondary Effectiveness Endpoint[1]	Bulkamid	Control
Proportion of subjects dry according to the ICIQ-UI questionnaire	13.7%	14.6%
Change from baseline in the average daily number of incontinence episodes (stress, urge, and all urinary incontinence episodes) based on voiding diary[2]	-2.6 episodes	-2.1 episodes
Proportion of subjects with no SUI episodes based on voiding diary	45.6%	50.5%
Responder rate ("improved," "much improved" or "cured/dry") based on the subject perception of effectiveness	77.0%	70.3%
Change from baseline in IQoL score[2]	31.1 points	26.8 points
Change from baseline in ICIQ-UI score[2]	-6.9 points	-6.0 points

[1]Assessed using data from the 12-month follow-up visit
[2]Mean changes reported

The protocol specified descriptive analyses of the secondary effectiveness endpoints only (i.e., no hypothesis tests).

3. Subgroup Analyses
   The following preoperative characteristics were evaluated for potential association with outcomes: age, baseline pad weight, baseline number of incontinence episodes, duration of incontinence, number of pregnancies, and center. A stepwise logistic regression model was used to evaluate the impact of these subgroups and key covariates on the primary effectiveness endpoint, including age, baseline pad weight, baseline number of incontinence episodes, duration of incontinence, number of pregnancies, and center. This planned analysis did not result in any covariates remaining in the model. Therefore, none of these subgroups or covariates were found to influence the primary effectiveness endpoint.

4. Pediatric Extrapolation
   In this premarket application, existing clinical data were not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 42 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

There are two published systematic literature reviews reporting the clinical use of Bulkamid in the treatment of female stress urinary incontinence and mixed incontinence (Siddiqui 2017 and Kasi 2016). Table 11 summarizes the key information from these published review articles.

Table 11. Published Systematic Literature Reviews

Lead author	Siddiqui, et al. (2017)	Kasi, et al. (2016)
Objective	To assess the efficacy and safety of urethral bulking agents (primarily Bulkamid and a competitor device) in the treatment of female stress urinary incontinence.	To conduct a systematic review on the efficacy and safety of Bulkamid in the treatment of female stress urinary incontinence.
Number of articles / patients referenced	12 articles / 1363 patients	8 articles / 787 patients
Follow-up duration	1 month – 8 years	9 months – 2 years
Effectiveness summary	Bulkamid treatment improves patient quality of life, as measured using various incontinence-specific patient report outcomes.	The number of incontinence episodes (per day), and the amount of urine leakage (grams per day) were significantly reduced 1 year following treatment. Quality of life was significantly improved.
Safety summary	Bulkamid is well-tolerated in the majority of patients. The most frequent adverse events among patients receiving Bulkamid are: • UTI (11%), • implantation site pain (10%), • acute urinary retention (3%), • de novo urgency (2%), • dysuria (1%), • persistent urge urinary incontinence (1%), and • hematuria (1%)	The most frequent adverse events were: • injection site pain (4-14%), • transient urinary retention (2-14%), • UTI (3-7%), • hematuria (1-5%) and, • chronic urinary retention (1-3%)

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Gastroenterology/ Urology Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness endpoint was clinically significant (≥ 50%) reduction from baseline in both urine leakage (as measured by a 24-hr. pad weight test) and daily number of incontinence episodes (as documented in a voiding diary) at the 12-month follow-up visit. In an ITT analysis of Bulkamid subjects, 46.9% of women experienced 50% or greater improvement in both measures of continence 12 months after final injection. This result is statistically equivalent (i.e., non-inferior) to that of the control population. This analysis result was supported by sensitivity and tipping point analyses, verifying the non-inferiority of Bulkamid under a variety of missing data assumptions. Therefore, the pivotal study met the primary effectiveness endpoint success criteria. Subgroup analyses of the primary effectiveness endpoint were conducted assessing whether there are any differences in effectiveness outcome based on age, baseline pad weight, baseline number of incontinence episodes, duration of incontinence, number of pregnancies, and center. The subgroup analyses did not find any statistically significant differences in any of the groups.

Secondary effectiveness endpoint analyses investigated the proportion of Bulkamid subjects achieving dryness at 12 months (i.e., 23.7% determined from 24-hr. pad weight testing; 45.6% determined from voiding diary; 13.7% from the ICIQ-UI questionnaire), change from baseline in urine leakage as assessed in the 24-hr. pad weight test (i.e., mean decrease of 62.6g), change from baseline in the average daily number of incontinence episodes (i.e., mean decrease of 2.6 episodes), improvement in IQoL score (i.e., mean increase of 31.1 points) and ICIQ-UI score (i.e., mean decrease of 6.9 points), and patient self-reported improvement rate (i.e., 76.4% reporting at least "improved"). These results are consistent with those of the control population, and further demonstrate the effectiveness of Bulkamid.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies, as well as data collected in a clinical study conducted to support PMA approval as described above. The prespecified primary safety endpoint was the incidence of device- and procedure-related SAEs. The only such event that occurred in the study was a single procedure-related incident of hematuria in a Bulkamid subject, which is an anticipated event and was readily resolved.

The safety profile of Bulkamid is favorable based on the outcomes of the pivotal study, and are similar to that of the control treatment. Overall, 26.3% of Bulkamid subjects experienced at least one device- or procedure-related adverse event, which were predominantly transient and mild. The most common adverse events reported were pain at implant site, acute retention, and UTI. Long-term risk information leveraged from published review articles further supported the safety profile of Bulkamid.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The benefit of Bulkamid treatment is a reduction in the amount and frequency of involuntary urine loss, which is a clinically meaningful endpoint. At 12 months, 46.9% (107/228) of Bulkamid patients met the study definition of success based on this effectiveness endpoint. The observed Bulkamid success rate was demonstrated to be non-inferior to that of the control population. In addition, improvement in subjective quality of life scores and high patient responder rate provide further evidence of probable benefit.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. Approximately one quarter of Bulkamid subjects experienced an adverse event during the 12-month post-injection period. These events were predominantly transient and mild, and were equivalent to those of the control treatment. Neither migration nor urethral erosion, both significant events reported with the use of other urethral bulking agents, were observed in the Bulkamid study population.

Uncertainty was present in the review of the benefits (i.e., related to the use of less stringent inclusion criteria for selecting the study population, and including all incontinence episodes (instead of only those that are stress-related) in the effectiveness analysis) and risks (i.e., related to questions regarding the details of the adverse event adjudication process). However, despite these uncertainties, the clinical study was sufficiently robust to demonstrate that Bulkamid is non-inferior to the control urethral bulking agent with respect to safety and effectiveness.

1. Patient Perspectives

   Patient perspectives considered during this review included:

   - Quality of life (Urinary Incontinence Quality of Life Scale (IQoL), International Consultation on Incontinence Modular Questionnaire – Urinary Incontinence (ICIQ-UI) Short Form)
   - Subject responder rate (self-report of improvement in urinary incontinence systems)

In conclusion, given the available information above, the data support that for adult women with stress urinary incontinence (SUI) due to intrinsic sphincter deficiency (ISD), the probable benefits outweigh the probable risks.

D. **Overall Conclusions**

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The results from the non-clinical and clinical evaluations support that a significant portion of the patient population for whom the device is intended can be expected to achieve clinically significant results.

Based on the clinical study results, it is reasonable to conclude that the clinical benefits of the use of Bulkamid in the treatment of SUI due to ISD in adult women, in terms of reductions in the amount of urine leakage and the number of incontinence episodes, outweigh the risks. In the indicated patient population, Bulkamid is non-inferior to the control urethral bulking agent with respect to safety and effectiveness.

XIV. **CDRH DECISION**

CDRH issued an approval order on January 28, 2020.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. **APPROVAL SPECIFICATIONS**

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. **REFERENCES**

1. Kasi, A.D., et al. Polyacrylamide hydrogel (Bulkamid) for stress urinary incontinence in women: A systematic review of the literature. Int. Urogynecol. J. 27(3), 367-375, 2016.

2. Siddiqui, Z.A., et al. Intraurethral bulking agents for the management of female stress urinary incontinence: A systematic review. Int. Urogynecol. J. 28(9): 1275-1284, 2017.