DE NOVO CLASSIFICATION REQUEST FOR EMBOSPHERE MICROSPHERES

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Prostatic artery embolization device.** A prostatic artery embolization device is an intravascular implant intended to occlude the prostatic arteries to prevent blood flow to the targeted area of the prostate, resulting in a reduction of lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH). This does not include cyanoacrylates and other embolic agents which act by *in situ* polymerization or precipitation, or embolization devices used in neurovascular applications (see 21 CFR 882.5950).

NEW REGULATION NUMBER: 21 CFR 876.5550

CLASSIFICATION: II

PRODUCT CODE: NOY

BACKGROUND

DEVICE NAME: Embosphere Microspheres

SUBMISSION NUMBER: DEN160040

DATE OF DE NOVO: August 3, 2016

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95700 Roissy-en-France, FRANCE

INDICATIONS FOR USE

Embosphere Microspheres are indicated for use in embolization of arteriovenous malformations, hypervascular tumors, including symptomatic uterine fibroids, and prostatic arteries for symptomatic benign prostatic hyperplasia (BPH).

LIMITATIONS

- Embosphere Microspheres are restricted to use by prescription only.

- Embosphere Microspheres are contraindicated in patients with:
  - presence of collateral vessel pathways potentially endangering normal territories during embolization;
  - large diameter arteriovenous shunts (i.e. where the blood does not pass through an arterial/capillary/venous transition but directly from an artery to a vein);
  - active urinary tract infection or prostatitis;
  - prostate cancer;
  - bladder cancer;
  - bladder atonia, neurogenic bladder disorder, or other neurological disorder impacting bladder function as the sole etiology of urinary dysfunction; or
  - urinary obstruction due to causes other than BPH, including urethral stricture.
- Serious radiation-induced skin injury may occur to the patient due to long periods of fluoroscopic exposure, large patient diameter, angled x-ray projections, and multiple image recording runs or radiographs. Refer to your facility's clinical protocol to ensure the proper radiation dose is applied for each specific type of procedure performed. Physicians should monitor patients that may be at risk.
- A thorough clinical evaluation should be performed on all patients presenting for embolization for BPH (e.g., urinalysis, digital rectal exam, symptom scores, prostate imaging, prostate-specific antigen test, and transrectal ultrasound) to rule out prostate cancer.
- Because of the tortuous vessels and duplicative feeding arteries in the pelvic area, extreme caution should be used when performing prostatic artery embolization (PAE). Complications of non-target embolization include ischemia of the rectum, bladder, scrotum, penis or other areas.
- When using Embosphere Microspheres for prostatic artery embolization, do not use microspheres smaller than 100 microns. It is recommended to use 300-500 microns.
- The effects of PAE on fertility have not been determined. Therefore, this procedure should not be performed on men wanting to father a child.
- Patients with known allergy to contrast medium may require corticosteroids prior to embolization.
- Additional evaluations or precautions may be necessary in managing periprocedural care for patients with the following conditions:
  - Bleeding diathesis or hypercoagulative state; and
  - Immunocompromise.
- Embolization with Embosphere Microspheres should only be performed by physicians who have received appropriate interventional embolization training in the region to be treated.
- Collateral circulation may be present and can dilate and supply adjacent arteries as resistance within the prostatic bed increases. Therefore, there is potential for severe complications with non-target embolization.
- There is an increased chance of retro-migration of Embosphere Microspheres into unintended blood vessels as prostatic artery flow diminishes. Embolization should be stopped when the vasculature surrounding the prostate can no longer be visualized but before complete stasis in the prostatic artery.
- Potential complications include:
  - Non-target embolization of the rectum, bladder, scrotum, penis, or other areas

- The most frequent post-procedure complication includes "Post-PAE Syndrome," which includes nausea, vomiting, fever, pelvic pain, burning sensation, dysuria, and frequent or urgent urination
- Skin burn (radiation exposure) from prolonged fluoroscopy time
- Blood in urine, semen, or stool
- Bladder spasm
- Urinary tract infection
- Urinary retention
- Constipation

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

Embosphere Microspheres are small, compressible, hydrophilic spheres of acrylic polymer and porcine-derived gelatin, provided sterile, non-pyrogenic in (b)(4) saline. They are available in six size ranges (40 µm - 1200 µm), in syringes (Figure 1) or vials. The syringes contain 1 mL or 2 mL of microspheres in 6 or 7 mL of saline, respectively, in a single unit packaging. Vials contain 1 mL or 2 mL of microspheres in 3 or 4 mL of saline, respectively, in a single unit packaging.

The microspheres are delivered to the target site via catheter under fluoroscopic control. The technological characteristics of the subject devices are identical to the legally marketed Embosphere Microspheres (K991549, K021397).

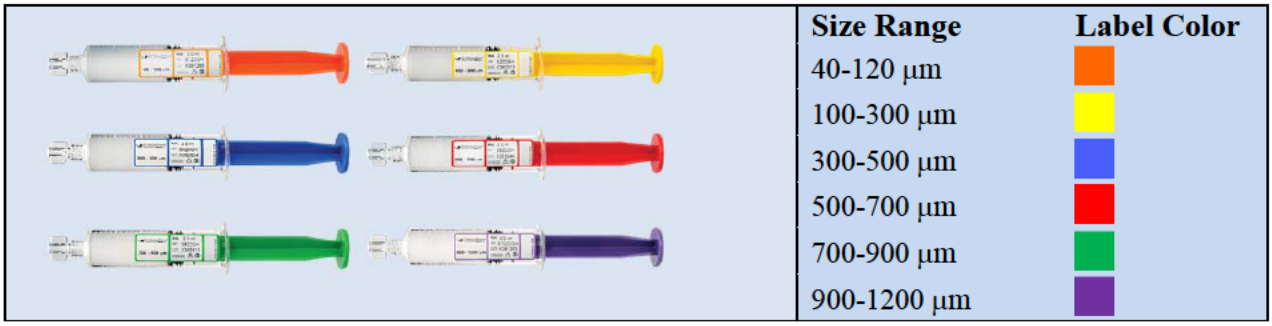

Figure 1. Embosphere Microspheres available in syringes (shown) or vials, color coded for each of the six separate size ranges, from 40 µm to1200 µm.

Usage:

Embosphere Microspheres are legally marketed for arterial embolization of arteriovenous malformations, hypervascular tumors, and symptomatic uterine fibroids. This De Novo request is for an expanded indication (new intended use) of embolization of prostatic arteries to treat BPH. The procedure of embolization of prostatic arteries is similar to embolization of uterine arteries except for the target location. Principles, materials and methods are the same. Both procedures involve arterial access through an artery (typically femoral or radial), using a guidewire and microcatheter under fluoroscopic guidance toward the prostatic artery. Once the

catheter tip is placed in the artery supplying the targeted tissue, Embosphere Microspheres mixed with a non-ionic contrast agent are delivered under fluoroscopic visualization to occlude the feeding vessel(s) to stop blood flow to the targeted area. Administration of microspheres continues just-prior-to or to stasis, with a dose that is prostate-volume dependent.

Mechanism of Action:

Embolization of the prostatic artery causes ischemic necrosis in the prostate, leading to a reduction in the size of the prostate and a reduction in lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH).

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

Biocompatibility testing was provided in previous premarket notifications, as shown in the table, below. All tests were passed, indicating that the device materials are biocompatible and appropriate for the new indication for use.

Table 1: Biocompatibility testing performed on Embosphere Microspheres.

Testing	**Result**	**510(k) numbers**
Cutaneous Irritation/corrosivity - Microsphere components	Passed	K991549; K021397
Intradermal Tolerance in rabbits & Systemic Toxicity in mice	Passed	K991549; K021397
Intracutaneous Injection Test	Passed	K991549; K021397
Systemic Injection Test	Passed	K991549; K021397
Lee and White Coagulation Test	Passed	K991549; K021397
In Vitro Hemocompatibility Test	Passed	K991549; K021397
Hemolysis-Rabbit Blood	Passed	K991549; K021397
Rabbit Pyrogen test	Passed	K991549; K021397
Cytotoxicity: L929 MEM Elution Test	Passed	K991549; K021397
Complement Activation Assay	Passed	K991549; K021397
Ames Mutation Assay	Passed	K991549; K021397
Kligman Maximization	Passed	K991549; K021397
Mouse Lymphoma Mutagenesis Test	Passed	K991549; K021397
Mouse Micronucleus Test	Passed	K991549; K021397
Toxicity test, 14-Day Repeated Does (Subacute)	Passed	K991549; K021397
Long Term Rabbit Intramuscular Implant Test (14 & 84 days)	Passed	K991549; K021397
Chronic Toxicity test in Rats (26 weeks)	Passed	K021397
Carcinogenicity Testing - In vivo Mouse Mutagenicity Test	Passed	K991549; K021397

SHELF LIFE/STERILITY

Embosphere Microspheres are steam sterilized by (b)(4) for (b)(4) at (b)(4) to achieve a Sterilization Assurance Level (SAL) of 10 . The sterilization cycle was validated using the (b)(4) in conformance with ISO 11134-1994, Sterilization of health care products - Requirements for validation and routine control - (b)(4), Sterilization of Medical Devices - Validation and Routine Control of Sterilization by Moist Heat.

Each batch of Embosphere Microspheres is tested for bacterial endotoxin using the Limulus Amebocyte Lysate (LAL) test with an acceptance threshold of 20 EU/container.

Embosphere Microspheres are labeled with a three-year shelf life and are intended for single use only. Three-year real time aging studies were conducted on Embosphere Microspheres in vial and in syringe to support the three-year shelf life.

Embosphere Microspheres are packaged in a sterile screw cap glass vial or in a sterile, plastic 20-mL syringe. Both packaging configurations are available with either 1.0 mL or 2.0 mL of microspheres in (b)(4) percent sterile, apyrogenic sodium chloride. The distal male Luer lock of the syringe is compatible with a catheter female Luer lock and a three-way stopcock female Luer lock according to the ISO 594 Luer standards. The syringe is preprinted with volume markings at 1-mL increments. Prior to sterilization, both the vials and syringes are placed into autoclavable packs with Tyvek lids. The box and inner package labels are color coded to identity the microsphere size.

MAGNETIC RESONANCE (MR) COMPATIBILITY

Embosphere Microspheres are made of (b)(4) polymer impregnated with porcine gelatin and have no ferrous composition.

PERFORMANCE TESTING – BENCH

Table 2: Bench performance testing performed on Embosphere Microspheres.

PARAMETERS	RESULTS
Size distribution	Laser light scattering measurement of size distribution, with low dispersion around the mean (19%)
Test injections in microcatheters	Ease of injection through small microcatheters with no tendency to clog through the formation of aggregates

PERFORMANCE TESTING – ANIMAL &/OR CADAVER

Animal testing has been performed and reported in the literature to evaluate the safety and feasibility of prostatic artery embolization (PAE) using Embosphere Microspheres. There have been three investigations of PAE using Embosphere Microspheres in animal models published in peer-reviewed journals.

Sun and colleagues[1] used 16 healthy pigs (n=8 embolization group, n=8 experimental group) to evaluate the technical feasibility, safety, and effect on sexual function of PAE. Eight experimental group animals underwent embolization with 500-700 μm Embosphere Microspheres. The pigs were checked 1-2x daily for a week for possible embolization-related adverse events. Observation of sexual activity was done for three months post-embolization and was rated on a scale of 0-3: 0 for no exhibited sexual behavior; 1 if the pig attempted to mount its partner; 2 if the male had an erect penis during attempted mounting; and 3 when the male achieved intromission and ejaculation. Subsequently, the animals were euthanized and investigators performed necropsy and pathologic examination. PAE was technically successful in all eight animals without complications. In the week post embolization, there were no incidences of acute urinary retention, peritonitis, skin or muscle ischemic necrosis in the perianal or buttock regions, or lameness in the hind legs. Wilcoxon rank sum testing revealed no significant difference in sexual function between the treatment and control groups ($p=0.328$). During necropsy, the bladder, ureters, deferent ducts, urethra, sigmoid colon, and rectum appeared to be normal in all animals. The prostates of the embolization group animals were pale and deformed compared to those of the control animals. The mean prostate volume of the treated animals was 3.9 mL compared to 7.3 mL for the control group, a statistically significant difference ($p<0.001$). Histologic examination revealed that Embosphere Microspheres had occluded the arterioles of the prostate, which resulted in disappearance of the partially normal gland structure in the surrounding area with replacement by fibrotic tissue and atrophy of residual glandular tissue. The authors concluded that PAE can be performed safely in pigs, producing decreased prostate volume without compromise of the animals' sexual desire or function.

Sun and colleagues[2] also evaluated pathologic responses and technical safety of PAE in 10 adult beagles (N=7, embolization group; N=3, control group). All animals underwent transrectal ultrasound (TRUS), then were surgically castrated. One month post castration, they were given hormone therapy for 4 months to induce BPH (confirmed with TRUS). After hormone administration, all dogs had repeat ultrasound and selective angiography, 4 had MRI, and the 7 beagles in the treatment group underwent PAE with 300-500 μm Embosphere Microspheres. One month after embolization or arteriography (controls), all dogs were sacrificed and investigators performed necropsy and pathologic evaluation. All 7 embolizations were technically successful. In the week post embolization, there were no incidences of acute urinary retention, signs of peritonitis, skin or muscle ischemic necrosis in the perianal or buttock regions, or hind limb lameness. Compared to baseline, the mean volume of the prostates 1 month after castration/pre-hormone treatment was significantly decreased ($p<0.001$). After 3 months of hormone therapy, the mean prostate

1. Sun F, Sanchez FM, Crisostomo V, et al. Benign prostatic hyperplasia: transcatheter arterial embolization as potential treatment−preliminary study in pigs. Radiology 2008; 246(3):783-89.
2. Sun F, Sanchez FM, Crisostomo V, et al. Transarterial prostatic embolization: initial experience in a canine model. AJR 2011; 197:495-501.

volume was significantly increased ($p<0.001$) compared to post-surgery. One month post embolization, 4 of the 7 dogs demonstrated prostate volume decreases of 33.7- 68.3%. The remaining 3 beagles that underwent PAE showed increases of 142.4-177.3%. During histopathologic examination the ureters, seminal vesicles, deferential ducts, bladder, urethra and sigmoid colon of all dogs appeared normal. Necropsy revealed no necrosis or damage in the internal or external urethral sphincter. There were intraprostatic cavities in the central areas of both lobes, lined with atrophied glands and fibrosis, in the prostates of all beagles that had been embolized. Of the 3 animals whose prostate diameters had become enlarged after PAE, 1 had complete cavity formation without residual gland along the inner cystic wall, and the other 2 had large cavities with less than 10% residual glandular tissue. The prostates of the 3 control dogs showed massive hyperplasia with extensive acinar dilatation lined by prominent hypertrophied epithelial cells. The authors concluded that PAE can be performed successfully in a canine model of hormone-induced benign prostatic hyperplasia.

Brooks and colleagues[3] examined the influence of embolic size on perfusion changes seen post PAE using dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI), in a canine model. DCE MRI is an accepted imaging modality for evaluation of perfusional changes after transarterial embolization. Three cohorts of 4 beagles each underwent PAE with 100-300 μm (Group A), 300-500 μm (Group B), or 500-700 μm (Group C) Embosphere Microspheres. Within 2 days prior to PAE and 1 month afterward, all dogs underwent DCE MRI for assessment of volume and perfusion. All beagles had volume analyses before and after embolization. The amount of necrosis seen by imaging in each cohort after PAE was small: in the group treated with 100-300 μm Embospheres, 3 out of 4 beagles demonstrated necrosis at an average of 2.5% + 2.1% of prostate volume; of the 4 dogs treated with 300-500 μm microspheres, only 1 demonstrated 0.8 + 1.6% volume reduction by necrosis; and 2 out of 4 beagles treated with 500-700 μm microspheress had an average of 1.3 + 1.8% necrosis of the prostate volume. There was no statistical significance between groups. A decrease in the volume of prostate lobes occurred in 11 of the 12 beagles. Remaining prostate volume averaged 77.1% in Group A, 55.9% in Group B, and 55.6% in Group C. The lesser degree of decrease in size for Group A compared to Groups B and C was statistically significant ($p=0.02$). In one animal in the 100-300 μm treatment group, the necrosis appeared to be confluent with the urethra, and was thought to represent a prostaticourethral fistula. The authors concluded that DCE MRI was feasible to monitor post-embolization changes after PAE in dogs, and that their morphological and perfusional assessments suggested embolic size of 500-700 μm is preferred when treating canine BPH.

These animal studies, conducted in porcine and canine models, provided preliminary evidence to help establish the technical feasibility, safety and effectiveness of using Embosphere Microspheres in the prostate artery embolization procedure.

3. Brook OR, Faintuch S, Brook A,et al. Embolization therapy for benign prostatic hyperplasia: influence of embolization particle size on gland perfusion. J Magn Reson Imaging 2013; 38:380-7.

SUMMARY OF CLINICAL INFORMATION

The De Novo request presents the outcomes of two categories of studies:

- Published literature studies (listed below) and manuscripts submitted for publication; and
- Prospective clinical studies.

Published Clinical Studies

Carnevale FC, Antunes AA, da Motta Leal Filho JM, et al. Prostatic artery embolization as a primary treatment for benign prostatic hyperplasia: preliminary results in two patients. Cardiovasc Intervent Radiol 2010; 33(2):355-61. DOI 10.1007/s00270-009-9727-z.

Carnevale FC, da Motta Leal Filho JM, Antunes AA, et al. Midterm follow-up after prostate embolization in two patients with benign prostatic hyperplasia. Cardiovasc Intervent Radiol 2011; 34(6):1330-3. DOI 10.1007/s00270-011-0136-8.

Antunes AA, Carnevale FC, da Motta Leal Filho JM, et al. Clinical, laboratorial, and urodynamic findings of prostatic artery embolization for the treatment of urinary retention related to benign prostatic hyperplasia. A prospective single-center pilot study. Cardiovasc Intervent Radiol 2013; 36(4):978-86. DOI 10.1007/s00270-013-0611-5.

Carnevale FC, da Motta Leal Filho JM, Antunes AA, et al. Quality of life and clinical symptom improvement support prostatic artery embolization for patients with acute urinary retention caused by benign prostatic hyperplasia. J Vasc Interv Radiol 2013; 24(4):535-42.

Camara-Lopes G, Mattedi R, Antunes AA, et al. The histology of prostate tissue following prostatic artery embolization for the treatment of benign prostatic hyperplasia. Int Braz J Urol 2013; 39(2):222-7.

Frenk NE, Baroni RH, Carnevale FC, et al. MRI findings after prostatic artery embolization for treatment of benign hyperplasia. Am J Roentgenol 2014; 203(4):813-21.

Moreira AM, Marques CFS, Antunes AA, et al. Transient ischemic rectitis as a potential complication after prostatic artery embolization: case report and review of the literature. Cardiovasc Intervent Radiol 2013; 36(6):1690-4.

Grosso M, Balderi A, Arnò M, et al. Prostatic artery embolization in benign prostatic hyperplasia: preliminary results in 13 patients. Radiol Med 2014; 120(4):361-8.

Kurbatov D, Russo GI, Lepetukhin A, et al. Prostatic artery embolization for prostate volume greater than 80 cm3: results from a single-center prospective study. Urology 2014; 84(2):400-4.

Russo GI, Kurbatov D, Sansalone S, et al. Prostatic arterial embolization vs open

prostatectomy: a 1-year matched-pair analysis of functional outcomes and morbidities. Urology 2015; 86(2):343-8.

de Assis AM, Moreira AM, de Paula Rodrigues VC, et al. Prostatic artery embolization for treatment of benign prostatic hyperplasia in patients with prostates > 90 g: a prospective single-center study. J Vasc Interv Radiol 2015; 26(1):87-93.

Laborda A, de Assis AM, Ioakeim I, et al. Radiodermitis after prostatic artery embolization: case report and review of the literature. Cardiovasc Intervent Radiol 2015; 38(3):755-9.

Bhatia S, Kava B, Pereira K, et al. Prostate artery embolization for giant prostatic hyperplasia. J Vasc Interv Radiol 2015; 26(10):1583-5.

Amouyal G, Thiounn N, Pellerin O, et al. Clinical results after prostatic artery embolization using the PErFecTED technique: a single-center study. Cardiovasc Intervent Radiol 2015; 39(3):367-75.

Lin YT, Amouyal G, Thiounn N, et al. Intra-vesical prostatic protrusion (IPP) can be reduced by prostatic artery embolization. Cardiovasc Intervent Radiol 2016; 39(5):690-5.

Khayrutdinov ER, Zharikov SB, Vorontsov IM, et al. Our first experience with prostatic artery embolization via transradial access. Cardioangiology 2015; 41:32-5.

Kably I, Pereira K, Chong W, et al. Prostate artery embolization (PAE) in the management of refractory hematuria of prostatic origin secondary to iatrogenic urological trauma: a safe and effective technique. Urology 2016; 88:218-21.

Carnevale FC, Iscaife A, Yoshinaga EM, et al. Transurethral resection of the prostate (TURP) versus original and PErFecTED prostate artery embolization (PAE) due to benign prostatic hyperplasia (BPH): preliminary results of a single center, prospective, urodynamic-controlled analysis. Cardiovasc Intervent Radiol 2016; 39(1):44-52.

Studies with Prospective Data

Three prospective studies have a total of 34 PAE subjects to date who have baseline data, have been treated with PAE, and have had at least one follow up evaluation:

Table 3: Studies with Prospective Data

	Study Design	**Number of Subjects Planned**	**Treated Subjects with follow up data available**
1.	Multi-center, prospective, randomized controlled study comparing PAE vs TURP	124 PAE 62 TURP	28 PAE 6 TURP
2.	Single-center, single-arm, open-label investigation of PAE for BPH	30	2
3.	Open-label, prospective, randomized study of PAE before radical prostatectomy	20 (10 PAE, 10 w/o)	4

1. Prospective, Controlled Investigation of Prostate Artery Embolization (PAE) with Embosphere Microspheres Compared to Transurethral Resection of the Prostate (TURP) for the Treatment of Symptomatic Benign Prostatic Hyperplasia (BPH)

Design: This is an ongoing phase 3 multicenter, prospective study designed to evaluate the safety and effectiveness of treating patients with symptomatic BPH with PAE using Embosphere Microspheres compared to conventional TURP.

Primary Endpoint: The primary endpoint will be improvement of symptoms from BPH evaluated using the International Prostate Symptom Score (IPSS) at 12 months post treatment. Improvement is defined as a decrease of at least 3 points. Secondary analysis includes a change of at least 1 category.

Major Inclusion Criteria: age 50-79; IPSS > 13; prostate size 50-90 g.
Major Exclusion Criteria: acute urinary retention requiring indwelling catheter; pelvic surgery or radiation

Follow Up: Months 1, 3, 6, and 12. At each of these visits patients complete the IPSS and International Index of Erectile Function (IIEF) questionnaires and have a physical exam, laboratory assessments (including the prostate-specific antigen (PSA) test), a digital rectal exam (DRE), and a transrectal ultrasound (TRUS) of the prostate. At each visit patients will have a cystoscopy and/or proctoscopy if medically indicated. An MRI of the prostate is conducted at the 3 and 12 month visits. Uroflowmetry testing is performed at the 1 and 12 month visits, and at other visits if medically indicated.

Patients will continue to be followed annually for up to 4 additional years. At a minimum, patients will be requested to complete the IPSS and IIEF questionnaires by telephone, email or mail once per year during this long term follow up period.

Safety: Safety is evaluated throughout the initial 12 months of the study by assessing adverse events.

Data Analysis: There are 28 PAE and 6 TURP evaluable patients from this study. All analyses were performed on the evaluable population, defined as all enrolled patients who received study treatment and for whom data from at least one follow up visit are available. Patients who had been enrolled but not treated, treated but not yet evaluated in a follow up visit, or refused treatment after enrollment were not included in the analyses.

Table 4: Results

Variable	**PAE (mean ± SD)**	**n**		**TURP (mean ± SD)**	**n**
Age yrs	63.1 ± 7.1	28		62.0 ± 7.0	6
IPSS	26.4 ± 5.6	28		29.0 ± 6.0	6
Quality of life	5.1 ± 1.0	28		5.2 ± 1.3	6
Qmax (mL/s)	6.9 ± 4.0	27		8.5 ± 4.2	6
PVR (mL)	182 ± 183	28		127 ± 176	6

Pdet (mmH_2O)	101.4 ± 90.3	26		74.0 ± 37.4	6
Total IIEF	29.0 ± 19.8	28		47.3 ± 26.9	6
Erectile function	11.5 ± 9.4	27		19.7 ± 12.0	6
Orgasmic function	4.2 ± 3.7	28		5.2 ± 4.2	6
Sexual desire	5.4 ± 2.4	27		7.7 ± 2.9	6
Intercourse satisfaction	4.1 ± 4.6	28		7.7 ± 6.6	6
Overall satisfaction	4.6 ± 2.8	26		8.4 ± 2.2	5
Prostate volume (g)	66.4 ± 12.0	28		62.7 ± 13.2	6
PSA (ng/mL)	4.0 ± 2.9	28		3.3 ± 3.6	6
Free PSA (%)	20.2 ± 11.0	25		21.8 ± 9.7	2

PVR - Post Void Residual (volume)
Pdet - Detrusor pressure

- 93% underwent bilateral embolization.
- TURP subjects typically admitted to the hospital (mean Length of Stay (LOS) = 32.2 hr); PAE subjects typically performed as outpatient (mean LOS = 23.1 hr).
- Post-treatment catheterization time was identical for both groups at 24.2 hr.
- At 3 months, 96% of PAE subjects achieved ≥ 3 point improvement in IPSS (n = 24).
- At 6 months, 91% of PAE subjects achieved ≥ 3 point improvement in IPSS (n = 22).
- At 12 months, 100% of PAE subjects achieved ≥ 3 point improvement in IPSS (n = 10).
- The mean IIEF score was higher for the TURP group at baseline, but within a normal range for both the surgery and embolization patients. Both arms demonstrated a trend toward improvement overall and in sub-scores during the follow up period.

Adverse Events: Adverse events during the study were predominantly mild. There are over 4 times as many PAE patients as TURP, so the overall incidence rate of events is proportional to the size of the cohort represented. The most common events among patients who underwent embolization were transient dysuria, bladder spasm, hematuria, hematospermia, nausea and fever. The last 2 are typical of post embolic syndrome common to all embolization procedures. The most frequent adverse events for surgery patients were dysuria and hematuria.

There were 123 adverse events in the PAE group of 28 subjects, 86% were classified as Mild. Severe adverse events among PAE patients included: urinary retention, sepsis, fever, UTI, rigors, and nausea in one patient each. One bladder injury was reported, but not classified as severe. There was one procedure-related serious adverse event (UTI) in the PAE group. There were 28 adverse events in the TURP group of 6 subjects, 86% were classified as Mild. The single severe adverse event among TURP patients was an episode of impacted stool. Total adverse events are provided in the table below without attribution as to severity or relatedness.

Table 5: The most frequent pertinent adverse events in the PAE group.

• Renal/Urinary disorders - Dysuria (18) - Bladder spasm (4) - Hematuria (4) - Hematospermia (4) - Micturition urgency (3)	• GI disorders - Nausea (5) - Constipation (3) - Hematochezia (2) - Abdominal rigidity (2) - Abdominal pain, upper + lower (1 each)

- UTI (3) - Bladder discomfort (2) - Urinary incontinence (2) - Urinary retention (2) - Pelvic pain (2) - Bladder injury (1) - Penile burning (1) - Penile pain (1) - Perineal pain (1) - Prostatitis (1) - Testicular pain (1) - Varicocele (1) - Hydrocele (1)	- Anorectal discomfort (1) - Vomiting (1) • General disorders - Pyrexia (4) - Suprapubic pain (2) - Pain (1) - Catheter site inflammation (1) - Chills (1) - Sepsis (1) - Cellulitis + localized infection (1 each) - Flank pain (1)

Table 6: The most frequent pertinent adverse events in the TURP group.

• Renal and urinary disorders - Dysuria (3) - Hematuria (3) - Incontinence (1) - Urinary incontinence (1) - Micturition urgency (1) - Ejaculatory disorder (1) - Retrograde ejaculation (1)	• GI disorders - Constipation (1) - Fecaloma (1) - Hemorrhoids (1) - Nausea (1) - Vomiting (1)

2. Phase II, Single-Center, Single-Arm, Open-Label Investigation of Prostate Artery Embolization (PAE) as a Treatment for Benign Prostatic Hyperplasia (BPH) in Men with Prostates Larger Than 90 Grams.

Design: This is a phase II, single center, prospective, single arm, investigational study to evaluate the safety and efficacy of PAE for treatment of severe lower urinary tract symptoms (LUTS) related to BPH in patients with prostate size between 90 grams and 200 grams that either refuse surgical treatment or are considered poor candidates for traditional surgical therapy. Thirty patients will be enrolled in the single treatment arm.

Primary Endpoint: To evaluate improvement of BPH symptoms as assessed by the IPSS at 12 months post PAE.

- Secondary objectives of the study include evaluating changes from baseline in prostate size, peak urine flow rate, post void residual urinary volume, detrusor muscle pressure, erectile function, and PSA, as well as PAE-related and overall adverse events.
- Tertiary objectives, collected for informational purposes, include total duration of the PAE procedure, total fluoroscopy time, type and volume of contrast media delivered, volume of embolic delivered, number of origins of prostatic supply, and duration of hospitalization and catheterization post PAE.

Major Inclusion Criteria: age 40-89; prostate size 90 – 200 g; IPSS $\geq$ 13.
Major Exclusion Criteria: pelvic surgery or ablative therapy; rectal cancer; clinically significant cardiac disease, uncontrolled diabetes mellitus, respiratory disease or immunosuppression.

Follow Up: After treatment, patients return for follow-up visits at 1 month, 3 months, 6 months, and 12 months post PAE. At each of these visits, patients complete IPSS and IIEF questionnaires, undergo a physical exam and transrectal ultrasound, and perform a medication review. Repeat MRI and urodynamic testing are performed at the 6 month and 12 month post PAE follow-up visits. Safety is evaluated throughout the initial 12 months of the study by assessing adverse events and findings on physical examination. Concomitant medication usage is reviewed at each study visit.

Data Analysis: As of July 1, 2016, 2 patients have been treated with PAE. Data from these patients is included in the composite database.

Results: The first patient was age 69, with a baseline IPSS of 32, quality of life 5, IIEF 5, and PSA of 3.42 mg/mL. His prostate was 145 g by MRI. He underwent bilateral embolization, and 6 month follow up evaluations showed that his IPSS had improved to 9, quality of life to 2, and IIEF to 8, with a PSA of 2.03 ng/mL. An MRI performed per protocol at 3 month follow up demonstrated that his prostate size had been reduced to 100 g.

The second patient, age 66, had baseline values of IPSS 23, quality of life 4, IIEF 67, and PSA 1.78 ng/mL. Prostate size by MRI was 93 g. After bilateral embolization his 6 month follow up exams revealed that his IPSS had improved to 6, quality of life to 2, and that his IIEF score was similar to baseline at 66. The size of his prostate as measured by MRI at the 3 month follow up visit was reduced to 77 g.

No adverse events were reported.

3. Phase II, Open-Label, Investigation of the Safety and Efficacy of Pre-operative Prostate Artery Embolization (PAE) Before and After Radical Prostatectomy in Prostate Cancer Patients.

Design: This is a phase 2, prospective, non-randomized, matched-pair, single center study designed to evaluate the safety and efficacy of PAE using Embosphere Microspheres as a pre-operative tool in patients with biopsy-proven adenocarcinoma of the prostate with localized disease. A total of 10 patients with biopsy-proven prostate carcinoma with localized disease will be enrolled in the study to receive pre-prostatectomy PAE, and matched with 10 controls who will not receive pre-prostatectomy PAE.

Primary Endpoint: The primary objective of the study is to evaluate estimated blood loss during robot-assisted laparoscopic radical prostatectomy (RALRP) among patients who receive pre-operative PAE and those who do not.

Secondary Objectives: The secondary objectives of the study include evaluation of changes in hemoglobin and hematocrit on post-operative day 1; change in prostate volume at 6 weeks post PAE; blood transfusion requirements during RALRP; RALRP procedure duration and length of hospitalization for RALRP; histologic changes in the prostate after PAE; presence or absence of a complete surgical margin around the adenocarcinoma as determined by histopathology examination post RALRP; change in PSA at 6 weeks post PAE; biochemical recurrence of

prostate cancer at 1 year post RALRP; return to continence post RALRP; RALRP-related adverse events; PAE-related adverse events; and erectile function at 1 year post RALRP.

Major Inclusion Criteria: age 45-79; biopsy-proven prostate adenocarcinoma with localized disease; be a candidate for RALRP; prostate size > 40 g.
Major Exclusion Criteria: cardiac disease; uncontrolled diabetes mellitus, respiratory disease, or immunosuppression that has required hospitalization in the past 6 months; history of pelvic irradiation or radical pelvic surgery; previous rectal surgery or history of rectal disease; history of any invasive treatment to the prostate; and acute urinary retention.

Follow Up: MRI, Expanded Prostate Cancer Index Composite (EPIC), and IIEF at baseline. After PAE treatment, patients return for follow-up visits at 2 weeks (± 4 days) and 6 weeks (± 2 weeks) post embolization. At the visit 2 weeks post PAE all patients undergo cystoscopy and rectoscopy, and at 6 weeks they complete the EPIC and IIEF questionnaires, receive a physical exam, and undergo laboratory assessments (including PSA levels), DRE, TRUS and an MRI of the prostate. The patients undergo RALRP at 10 weeks (±2 weeks) post PAE, and have first post-op follow up visit at 12 days ± 7 days for urinary catheter removal.

Once the cohort of patients to receive PAE has been enrolled, a similar cohort of patients will be enrolled who will undergo RALRP without preoperative PAE. These controls will be matched 1:1 to PAE patients according to American Urological Association (AUA) risk stratification guidelines as follows:

- Low risk: Stage T1c to T2a tumors, AND PSA ≤ 10 ng/mL, AND Gleason score ≤ 6
- Intermediate risk: Stage T2b tumors, OR PSA > 10 ng/mL but ≤ 20 ng/mL, OR Gleason score 7
- High risk: Stage T2c or higher tumors, OR PSA > 20 ng/mL, OR Gleason score 8-10

At 12 ± 7 days following PAE, all patients undergo a physical exam, blood and urine tests, pad weight test to assess urinary incontinence, a review of concomitant medications and adverse events, and urinary catheter removal. At subsequent follow-up visits at 3, 6, 9, and 12 months post RALRP ± 2 weeks, all patients undergo a physical exam, PSA assessment, pad weight test, complete the EPIC and IIEF questionnaires, and review concomitant medications and adverse events. All patients will be followed according to the institutional standard of care after completing their 12-month follow-up visit.

Data Analysis: As of July 1, 2016 4 patients had been treated with PAE. All patients in this investigation had benign prostatic hyperplasia, but this study is different from the others in that the primary goal was to reduce blood loss during robot-assisted laparoscopic radical prostatectomy for cancer, rather than to treat the BPH. The trial is of particular interest, despite the small number of current patients, because all 4 had cystoscopy and proctoscopy after PAE as well as surgery.

Results: Patient 1: 68 years old, with a prostate size of 164 g on baseline MRI and diagnosis of Gleason 6 (patterns unspecified) prostate cancer. At 2 weeks post unilateral PAE (right side embolized), cystoscopy was notable for erythematous lesions seen diffusely throughout bladder, but otherwise normal, and sigmoidoscopy was normal except for a 3 mm sessile polyp in the rectum. At 7 weeks following PAE, prostate size was reduced to 136.4 g on MRI. RALRP with

bilateral pelvic lymph node dissection performed 8 weeks following PAE showed no adhesions and decreased bleeding from the right side pedicle. Total blood loss was estimated at 120 mL. The patient remained stable and afebrile following the procedure and was discharged home on post-operative day 1.

Patient 2: 69 years old, with a prostate size of 103.3 g on baseline MRI, history of colon cancer treated by ascending colon resection 16 years previously, and current diagnosis of Gleason 6 (3+3) prostate cancer. At 2 weeks post bilateral PAE, cystoscopy was normal and sigmoidoscopy was normal, except for a 10 mm sessile polyp in the rectum (removed with a hot snare). At 6 weeks following PAE, prostate size was reduced to 70.9 g on MRI. RALRP with bilateral lymph node dissection performed 8 weeks following PAE was complicated by adhesions from prior colectomy, but no new adhesions involving the prostate were observed. Total blood loss was estimated at 120 mL.

Patient 3: 75 years old, with a prostate size of 102 g on baseline MRI, and diagnosis of Gleason 7 (3+4) intraductal and adenocarcinoma of the prostate. At 2 weeks post bilateral PAE, cystoscopy and sigmoidoscopy were both normal. At 6 weeks following PAE, prostate size was reduced to 93 g on MRI. RALRP with bilateral lymph node dissection performed 8 weeks following PAE showed no adhesions and total blood loss was estimated at 100 mL.

Patient 4: 81 years old, with a prostate size of 126.0 g on baseline MRI and diagnosis of Gleason 6 (patterns unspecified) prostate cancer. At 2 weeks post bilateral PAE, cystoscopy was notable for nondescript "oozing" in the prostatic urethra and sigmoidoscopy was normal. At 6 weeks post PAE, prostate size was reduced to 65.9 g on MRI. RALRP with pelvic lymph node dissection performed 8 weeks following PAE showed adhesions along the right lower quadrant, but these were managed intraoperatively without complication. Total blood loss was estimated at 100 mL. The patient remained stable and afebrile following the procedure and was discharged home on post-operative day 1.

No adverse events were reported. There were no unanticipated adverse events noted in any of the three prospective studies.

Composite Database

This consisted of raw, patient level data from the authors of as many of the papers as possible, as well as from investigators of independent studies when accessible, and prospectively collected clinical treatment outcome data from physicians in geographies in which PAE is an approved indication.

- Data from 4 international sites (São Paulo, Brazil; Paris, France; Cuneo and Milan, Italy).
- 10 publications, 3 manuscripts in preparation for publication, and two studies in the U.S. investigating safety/efficacy of prostatic artery embolization with Embosphere Microspheres.
- Includes data from a Merit/BioSphere PAE for BPH study and other investigational studies.
- Patients discussed in more than one publication are included only once in the analyses.
- All patients for whom data were available for at least one follow-up window were included in the Composite database. Patients for whom baseline data were provided but follow-up data were missing (due to loss to follow-up or short duration of follow-up, since the PAE procedure) were not included in the Composite database.

Table 7: Patient counts from each site that contributed data to the composite database.

Source of data	**Number of patients with ≥ 1 follow up visit**
São Paulo, Brazil; PI: Francisco Carnevale MD	105
Milan, Italy; PI: Antonio Rampoldi MD	56
Cuneo, Italy; PI: Maurizio Grosso MD	31
Paris, France; PI: Marc Sapoval MD	60
Investigational Study; PI: ----	2
Investigational Study; PI: ----	4
Investigational Study; Merit Medical	28
TOTAL	**286**

Data Analysis: Because studies differed in variables they collected, the analyses focused on data that was common across all publications and clinical trials, namely IPSS, QOL, and prostate volume at baseline and two follow-up windows (1 to 3 months and 9 to 16 months).

- 89% of Composite subjects were able to undergo bilateral embolization.
- 97% of subjects at the 9-16 month window had a reduction of IPSS ≥ 3 points (93% at 31-3 months).
- 90% achieved ≥ 1 IPSS category improvement at 9-16 months (84% at 1-3 months).

Subgroups of Interest

In addition to the overall Composite population, analyses were done for subsets of patients age 80 or older, with prostates 90 g or larger, and those with indwelling catheters at baseline for management of acute urinary retention. Patients in these groups were of particular interest because they frequently are contraindicated for TURP: elderly patients have higher incidence rates of comorbid conditions, patients with prostate size larger than 90 g are typically referred for open surgery, and patients in acute retention are not generally treated by transurethral procedures. These categories are not mutually exclusive:

- Thirteen of 39 subjects age ≥ 80 years (33%) had indwelling catheters.
- 12 of 95 subjects with prostate ≥ 90 g (12.6%) had indwelling catheters.

Subjects age ≥ 80 years (N=39)

- Bilateral embolization performed in 80%.
- 89% of the 9 subjects each evaluated at the 1-3 months and 9-16 months windows experienced a ≥ 3 point improvement in IPSS.
- 78% at 1-3 months and 67% at 9-16 months experienced ≥ 1 category of improvement in IPSS.

Table 8: Mean IPSS at baseline and follow up of patients age ≥ 80 years. * p-value relative to baseline calculated by Paired Sample Signed-Rank Test.

Time Window	**Mean ± SD**	**n**
Baseline	23.9 ± 9.9	32
1 to 3 months f/u	13.4 ± 9.2	9
9 to 16 months f/u	7.0 ± 2.9	9

Prostate ≥ 90 g (N=95)

- 92% underwent bilateral embolization.
- 96% achieved ≥ 3 point improvement in IPSS at 1-3 months and 9-16 months.
- 87% of subjects at 1-3 months and 89% of subjects at 9-16 months experienced ≥ 1 category improvement in IPSS.

Table 9: Mean IPSS at baseline and follow up of patients with prostate size ≥ 90 g. * p-value relative to baseline calculated by Paired Sample Signed-Rank Test.

Time Window	**Mean ± SD**	**n**
Baseline	19.8 ± 6.8	87
1 to 3 months f/u	5.0 ± 4.6	69
9 to 16 months f/u	4.6 ± 4.1	54

Patients with indwelling catheters

- 82% were able to undergo bilateral embolization.
- Baseline IPSS data are unavailable for subjects with an indwelling catheter.

Table 10: Mean IPSS during follow up of patients with indwelling catheters at baseline.

Time Window	**Mean ± SD**	**n**
1 to 3 months f/u	6.0 ± 4.8	22
9 to 16 months f/u	5.9 ± 4.3	22

Table 11: Summary of outcomes for the Merit clinical study, Composite cohort, and subgroups of Composite cohort.

Variable	Study 1		Composite (n)	≥ 80 years (n)	≥ 90 grams (n)	Indwl Cath (n)
	PAE (n)	TURP (n)				
Age yrs	63.1 (28)	62.0 (6)	67.7 (286)	84.6 (39)	68.4 (95)	73.8 (54)
Baseline IPSS	26.4 (28)	29.0 (6)	21.5 (251)	23.9 (32)	19.8 (87)	--
Baseline QoL	5.1 (28)	5.2 (6)	4.8 (166)	4.6 (17)	4.6 (53)	5.8 (16)
Baseline Qmax (mL/s)	6.9 (27)	8.5 (6)	6.9 (175)	7.3 (4)	7.0 (63)	--
Embolization						
Bilateral	26 (92.9)	------	254 (88.9%)	31 (79.5%)	87 (91.6%)	44 (81.5%)
Unilateral	2 (7.1)	------	29 (10.1%)	8 (20.5%)	6 (6.3%)	9 (16.7%)
No data	0 (0)	------	3 (1.0%)	0 (0%)	2 (2.1%)	1 (1.8%)
IPSS						
Baseline	26.4 (28)	29.0 (6)	21.5 (251)	23.9 (32)	19.8 (87)	--
1-3 months	10.6 (24)	6.5 (6)	6.3 (190)	13.4 (9)	5.0 (69)	6.0 (22)
9-16 months	10.7 (10)	4.3 (4)	6.2 (136)	7.0 (9)	4.6 (54)	5.9 (22)
≥3 pt improvement						
1-3 months	0.958 (24)	1.000 (6)	0.931 (190)	0.889 (9)	0.955 (69)	--
9-16 months	1.000 (10)	1.000 (4)	0.967 (136)	0.889 (9)	0.961 (54)	--
Category change						
1-3 months	0.792 (24)	1.000 (6)	0.842 (190)	0.778 (9)	0.870 (69)	--
9-16 months	0.700 (10)	1.000 (4)	0.897 (136)	0.667 (9)	0.889 (54)	--
Quality of life						
Baseline	5.1 (28)	5.2 (6)	4.8 (166)	4.6 (17)	4.6 (53)	5.8 (16)
1-3 months	1.6 (24)	0.8 (6)	1.4 (165)	1.4 (8)	1.1 (49)	1.0 (25)
9-16 months	1.3 (10)	0.5 (4)	1.4 (116)	1.1 (10)	1.2 (40)	1.0 (23)
Prostate volume						
Baseline	66.4 (28)	62.7 (6)	85.1 (265)	78.1 (34)	124.2 (95)	79.0 (45)
1-3 months	52.1 (23)	28.2 (4)	62.4 (193)	55.1 (16)	85.9 (70)	64.3 (21)
9-16 months	49.7 (9)	31.7 (3)	65.2 (118)	64.6 (10)	91.0 (44)	54.3 (20)

As shown in Table 11 (above), IPSS and QOL scores demonstrate an improvement of symptoms after prostate artery embolization. This improvement occurs in the shorter-term (1-3 months) and longer-term (9-16 months), similar to the improvements in the TURP group. Similar symptom reductions are seen in the composite groups and the sub-groups (≥ 80 years, ≥ 90 grams).

Adverse Events: There were a total of 418 adverse events in 286 subjects. There were a total of 418 adverse events in 241/286 (85%) Composite Group subjects, and 3/286 (1%) had at least one severe adverse event.

Adverse events that occurred at a rate ≥ 2.5% were:

- Post-prostatic artery embolization syndrome, defined as mild pain in the perineum, retropubic area, and/or urethra; fever; nausea (74.1%)
- Dysuria (7.7%)
- Regional pain, including abdominal, upper; abdominal, lower; anorectal discomfort; pain; suprapubic pain; procedural pain; groin pain; bladder discomfort; urethral pain; pelvic pain; pelvic burning sensation; penile pain; perineal pain; testicular pain (7.3%)
- Hematochezia (4.9%)
- Decreased ejaculatory volume (4.9%)
- Hematospermia (4.2%)
- Hematuria (3.5%)
- Urinary retention (3.1%)
- Urinary tract infection (2.8%)
- Pyrexia (2.8%)

Serious Adverse Events Reported with the use of Embosphere Microspheres

- Dissection of inferior vesical artery (n=1, Carnevale et al., 2013 *JVIR* 24:535-42).
- Hematuria at 9 days with focal bladder wall ischemia noted on MRI at 30 days with spontaneous resolution at 90 days (n=1, Carnevale et al., 2013 *JVIR* 24:535-42).
- Transient ischemic rectitis (n=1, Moreira et al., 2013 *Cardiovasc Intervent Radiol* 36:1690-4).
- Radiodermatitis with PAE procedure time of 310 minutes in obese male with NON ST segment elevation acute cardiac syndrome, resolved with conservative therapy at 60 days (n=1, Laborda et al., 2015 *Cardiovasc Intervent Radiol* 38:755-9).
- Transient pubic bone ischemia noted coincidentally at 3 month MRI resolved spontaneously (n=1, Carnevale et al., 2016 *Cardiovasc Intervent Radiol* 39:44-52).

Fifteen of 286 subjects in the Composite Group (5%) required salvage TURP procedures for persistent symptoms. No complications during TURP were associated with having had prior PAE.

In addition to these subjects, four subjects underwent robotic-assisted laparoscopic prostatectomy following PAE. Adhesions along the right lower quadrant were noted in 1 patient that were managed intraoperatively. No other adhesions associated with PAE were noted.

LABELING

Embosphere Microspheres comply with the labeling requirements under 21 CFR 801.109 for prescription devices in the provided physician labeling. In addition, the labeling includes specific instructions regarding the proper preparation and use of the device to mitigate the risks of non-target ischemia and infection. The labeling also identifies the validated shelf life of the device.

The labeling also indicates that if the sterile barrier has been compromised, the device must not be used.

RISKS TO HEALTH

Table 12 below identifies the risks to health that may be associated with use of the prostatic embolization device and the measures necessary to mitigate these risks.

Table 12: Risks to health and corresponding mitigation measures.

Identified Risk	**Mitigation Measures**
Adverse tissue reaction	Biocompatibility evaluation
Infection	Sterilization validation Shelf-life validation Non-clinical performance testing Labeling
Non-target ischemia	Clinical data Non-clinical performance testing Labeling
Urinary retention	Labeling
Post-prostatic artery embolization syndrome (nausea, vomiting, regional pain, non-infectious fever, minor hematuria or hematochezia)	Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the prostatic artery embolization device is subject to the following special controls:

1. The device must be demonstrated to be biocompatible.

2. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
   a. Evaluation of suitability for injection through catheters intended for use in embolization; and
   b. Evaluation of the size distribution of the device.

3. Performance data must support the sterility and pyrogenicity of the device.

4. Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.

5. Clinical data must evaluate post-embolization damage due to non-target embolization under anticipated use conditions.

6. The labeling must include:
    a. specific instructions on safe device preparation and use;
    b. the device shelf life;
    c. data regarding urinary retention; and
    d. data regarding post-prostatic artery embolization syndrome.

BENEFIT/RISK DETERMINATION

The benefits and risks of Embospheres Microspheres are based on non-clinical and clinical data.

The effectiveness of PAE in treating symptomatic BPH is clinically relevant, and is on the order of the effect noted with TURP, a typical intervention for this condition. The IPSS reduction averaged 60% in Study 1 and 71% in the Composite Group. Similar reductions of 70-85% are quoted following TURP (Ahyai et al., 2010 Urology, 58:394-97; McConnell et al.: Benign prostatic hyperplasia: diagnosis and treatment. Clinical practice guideline no. 8. 1994 U.S. Department of Health and Human Services, Agency for Health Care Policy and Research, Public Health Service Rockville (MD) p. 1–17). Improvement in QOL following PAE is also clinically meaningful. While the decrease in prostate size is not as significant as would be expected following TURP, the relationship between prostate size and symptom relief is complex, and symptom relief is not completely explained by reduction in prostate size, alone. Furthermore, PAE seems effective in clinically relevant subgroups (older age, larger prostate, indwelling catheter) that might not be eligible or able to undergo more invasive procedures such as TURP.

The risks of the device are based on non-clinical laboratory and/or animal studies as well as data collected in clinical studies described above, and include: blood vessel perforation or rupture, unintended thrombosis (i.e., non-target embolization), adverse tissue reaction, infection, hematoma, risk of adverse events due to improper patient selection, and impact on subsequent surgical treatment of BPH. The safety of PAE does introduce safety concerns not present with other typical interventions for this condition (such as TURP), primarily related to embolization, in general, such as non-target embolization, hematoma, radiation exposure, etc. However, the data presented illustrated a low rate of these more serious events. Overall, the safety profile compares favorably to TURP, which has higher risks for blood loss and erectile dysfunction, typically with a longer length of hospital stay.

Additional factors to be considered in determining probable risks and benefits for the Embosphere Microspheres device include the fact that, of the clinical data, the Study 1 data set is the most reliable, but small in number. The small sample size of this population resulted in larger confidence intervals around the mean and greater statistical uncertainty, but the degree of uncertainty present is acceptable in light of the demonstrated overall benefit (improved symptoms, relative non-invasiveness) and minimal/moderate risk.

Patient Perspectives

Patient perspectives considered for the Embosphere Microspheres included quality of life (QOL) questionnaires such as the International Prostate Symptom Score (IPSS). The IPSS consists of 8 questions (7 regarding symptoms and 1 regarding quality of life) and is used as a screening, diagnostic and symptom tracking tool for BPH. Improvement is defined as a decrease of at least 3 points. All groups treated with BioSphere Embospheres showed a reduction in IPSS from baseline to follow-up at 9-16 months. In one of the investigational studies, 91% of PAE subjects achieved ≥ 3 point improvement in IPSS (n = 22) at 6 months while, at 12 months , 100% of PAE subjects achieved ≥ 3 point improvement in IPSS (n = 10). 97% of the composite group subjects at the 9-16 month window had a reduction of IPSS ≥ 3 points.

Benefit/Risk Conclusion

In conclusion, given the available information above, the data support that, for embolization of the prostatic arteries for symptomatic benign prostatic hyperplasia (BPH), the probable benefits outweigh the probable risks for Embosphere Microspheres. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the Embosphere Microspheres is granted and the device is classified under the following:

Product Code: NOY
Device Type: Prostatic artery embolization device
Class: II
Regulation: 21 CFR 876.5550