1 Protocol Synopsis

Title	Randomized trial of Barrigel® to increase distance between the rectum and prostate bed to decrease rectal dose in patients receiving moderately hypofractionated radiation therapy who have had recurrence of prostate cancer after post-prostatectomy
Short Title	Barrigel PPRT (Post-Prostatectomy Radiation Therapy) Trial
Investigational Device	Barrigel is an absorbable gel based on Non-Animal Stabilized Hyaluronic Acid (NASHA™) that is injected into the peri-rectal space.
Indication for Use	Barrigel is intended to temporarily position the anterior rectal wall away from the prostate or prostate bed during radiotherapy treatment for prostate cancer and, in creating this space, it is the intent of Barrigel to reduce the radiation dose delivered to the anterior rectum. Barrigel is composed of biodegradable material and maintains space for the entire course of prostate or prostate bed radiotherapy and is intended to be absorbed by the patient's body over time.
Study Objective	To evaluate the safety and effectiveness of Barrigel to reduce the radiation dose delivered to the anterior rectum by creating a space when injected between the rectum and the prostate bed in men receiving definitive external beam radiation therapy (intensity-modulated radiation therapy) for recurrence of prostate cancer after radical prostatectomy.
Study Design	A prospective, randomized, controlled, single-masked multicenter study.

Study Duration	Subject enrollment and data collection through the 36- Month Visit. Site and subject enrollment are expected to take 12 months, so three-month data will be submitted to FDA as part of a 510(k) within 15 months of first subject treated. Post 3-month data available at time of submission will also be provided in the 510(k). Once Barrigel is cleared for this indication, all subjects will continue to be followed for a total of 36 months in a post-market study in which they will be enrolled upon 510(k) clearance and subsequent termination of the IDE study.
Study Sites	Up to 15 US sites and up to 3 OUS sites.
Number of Subjects	84 randomized subjects (56 Barrigel; 28 Control); and At least 1 Barrigel training subject per site (up to 24 non- randomized subjects, analyzed separately)
Study Success	Study success will be achieved if the proportion of Barrigel subjects achieving a ≥25% reduction in the volume of rectum receiving 90% of the prescription dose is greater than a minimum clinically acceptable success rate of 70%.
Injection Procedure and Radiation Therapy Parameters	All subjects will have a transrectal ultrasound (TRUS) conducted. In the control subjects this will act as a sham procedure. For the investigational subjects, the TRUS will be used to visualize the placement of the needle. The investigational subjects will have Barrigel injected between the rectum and prostate bed. Radiation therapy must begin within 30 days after TRUS/Barrigel injection and will be administered using IMRT. The radiation prescription dose for all subjects will be 62.5 Gy in 25 fractions.
Primary Objective	Investigational subjects only: Achievement of a ≥25% reduction in the volume of rectum receiving 90% of the prescription dose.
First-Ranked Secondary Safety Objective	Test whether the use of the Barrigel spacer does not increase the incidence of acute grade 2+ GI toxicity within the first 3 months, which will be assessed using the proportion of subjects who have one or more incidences of acute grade 2+ GI toxicity within the first 3 months.

Second-Ranked Secondary Effectiveness Objective	Test whether the change in EPIC Bowel QOL Assessment score from Pre-injection to 3 months for Barrigel subjects is no worse than [non-inferior to] that of Control subjects.
Exploratory Effectiveness Endpoints	▪ Evaluate the change in EPIC Urinary Assessment composite score from baseline within 3 months after completion of radiation therapy ▪ Investigational subjects only: Change in the separation created between the posterior edge of the bladder and the anterior rectal wall between the Immediate post- injection and 3-month post-injection MRI scans ▪ Investigational subjects only: Change in the amount of Barrigel remaining in the space between the Immediate post-injection and 3-month post-injection MRI scans. ▪ Investigational subjects only: Differences in rectum, bladder, and penile bulb dose using the Pre-injection and Immediately Post-Barrigel injection CT and MRI simulation scans
Other Safety Endpoints	▪ All adverse events ▪ Investigational subjects only: Incidence of radiation therapy delay because of Barrigel-related adverse events.
Primary Effectiveness Endpoint Evaluation	The Core Dosimetry Lab will determine the reduction in radiation to the rectum based on the pre-injection and immediate post-Barrigel injection CT and MRI scans for all Barrigel subjects.

First-Ranked Secondary Safety Evaluation	Subjects will be evaluated for adverse effects (AEs) from the time of Barrigel injection through 3 month follow up visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Subjects will be evaluated during TRUS/Barrigel injection, weekly while receiving radiation therapy and at 3 months post-injection. A masked adjudication committee will review all-site reported adverse events and assess each adverse event for seriousness and relationship to the device and/or injection procedure according to AE review protocol.
Second-Ranked Secondary Effectiveness Evaluation	Subjects will be evaluated for changes in their Expanded Prostate Cancer Index Composite (EPIC) Bowel QoL score from the time of Barrigel injection through 3 month follow up visit. Subjects will be filling out the EPIC questionnaire at pre-injection, as well as 3, 6, 12, and 36 months follow up.
Inclusion Criteria	Subjects may participate in this study if all the following criteria are met: 1. Age ≥ 18 years 2. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 3. Prostatectomy surgeon notes specifying successful bilateral nerve Sparing procedure 4. Documentation of an intra or interfascial radical prostatectomy 5. Confirmed diagnosis of adenocarcinoma of the prostate treated primarily with radical prostatectomy with pN0 or pNX pathologic stage 6. No radiographic evidence of local, regional, or distant metastatic disease via PSMA PET or Axumin fluciclovine F18 scan 7. Prostate-specific antigen (PSA) >0.1 and ≤0.5 ng/mL at screening, or PSA ≤0.1 ng/mL with documentation of 3 consecutive PSA rises since prostatectomy, consistent with evolving biochemical recurrence. 8. Intent to receive definitive radiation therapy to the prostate bed 9. Written informed consent for study participation prior to study enrollment

Exclusion Criteria	A subject will be excluded from participating in this study for any of the following reasons: 1. Known allergy to hyaluronic acid 2. Pathologic T4 disease 3. Prior local prostate cancer therapy including cryotherapy or brachytherapy. 4. Prior post-prostatectomy or pelvic radiation therapy 5. Planned elective pelvic lymph node radiation therapy 6. Prior anorectal surgery (e.g. low anterior resection, abdominoperineal resection, absence of a rectum) 7. Inflammatory bowel disease requiring treatment with steroids (e.g. Crohn's disease, ulcerative colitis) 8. Active connective tissue disorder including lupus or scleroderma 9. Any urogenital abnormality that could limit the ability to access the Barrigel injection site 10. White blood cell count <4000/uL or >12,000/uL. 11. Hemoglobin <10 g/dL (transfusion or other intervention to achieve this is acceptable). 12. Active bleeding disorder or clinically significant coagulopathy defined as PTT >35 seconds or INR >1.4 or platelet count <100,000/mm3. 13. Serum AST/ALT >2.5 times the institutional upper limit of normal 14. Creatinine >2.0 mg/dL 15. Bilirubin >2.0 mg/dL 16. History of chronic renal failure. 17. History of uncontrolled diabetes (e.g. symptomatic hyperglycemia that is not controlled with medical management; fasting blood glucose >300 mg/dL). 18. History of acquired immunodeficiency syndrome (AIDS). Patients with controlled HIV infection (CD4+ T-cell counts ≥ 350 cells/μL) and no history of AIDS-defining opportunistic infections may be included. 19. Contraindication to having an MRI or PSMA/PET scan (e.g. non-MRI compatible device).

	20. Presence of bilateral hip implants, although unilateral hip implant may be permissible if the implant is MRI compatible and does not produce artifact that interferes with any requirements of the study protocol 21. Subject unable or unwilling to comply with study requirements 22. Any condition that in the investigator's opinion would prevent administration or completion of study therapy 23. Evidence of local, regional, or distant metastatic disease on any pelvic MRI obtained within the past 90 days
Ethical Considerations:	This study will be conducted under a protocol reviewed by an IRB as outlined in 21 CFR 56. The study will be conducted by scientifically and medically qualified persons. The benefits of the study are in proportion to the risks, the rights and welfare of the subjects will be respected, and the investigators conducting the study will ensure that the hazards do not outweigh the potential benefits. The investigators and sponsor will ensure that the results reported are accurate.
Informed Consent:	This study will be conducted in full compliance with the informed consent regulations in 21 CFR 50. All study subjects will be provided a consent form describing this study and providing sufficient information to make an informed decision about the subject's participation in this study.