BioProtect, Ltd.
% Janice Hogan
Partner
Hogan Lovells U.S. LLP
1735 Market Street, Floor 23
PHILADELPHIA, PA 19103

August 25, 2023

Re: K222972
Trade/Device Name: BioProtect Balloon Implant™ System
Regulation Number: 21 CFR 892.5725
Regulation Name: Absorbable perirectal spacer
Regulatory Class: Class II
Product Code: OVB
Dated: August 21, 2023
Received: August 21, 2023

Dear Janice Hogan:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part

801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Lora D. Weidner, Ph.D.
Assistant Director
DHT8C: Division of Radiological Imaging
and Radiation Therapy Devices
OHT8: Office of Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
K222972

Device Name
BioProtect Balloon Implant™ System

Indications for Use *(Describe)*

The BioProtect Balloon Implant System is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space it is the intent of the BioProtect Balloon Implant System to reduce the radiation dose delivered to the anterior rectum.

The BioProtect Balloon Implant System is composed of a balloon made of a biodegradable material that maintains the space for the entire course of prostate radiotherapy treatment and is completely absorbed by the patient's body over time.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

K222972

510(k) Summary

BioProtect Ltd.'s BioProtect Balloon Implant™

System

I. Contact Information

Submitter:

Janice Hogan
Hogan Lovells US LLP
janice.hogan@hoganlovells.com

Ph: (267) 675-4611

Sponsor:

BioProtect, Ltd.
8 Tsor St.,
Tzur Yigal
Israel, 4486200
Phone: +972 (9) 8667-891
Fax: +972 (9) 7731-932

II. Date of 510(k) Summary Preparation:

August 24, 2023

III. Subject Device

Trade name:	BioProtect Balloon Implant™ System
Common name:	Absorbable Perirectal Spacer
Classification name:	Absorbable Perirectal Spacer
Regulation Number	21 CFR 892.5725
Product code:	OVB
Regulatory class:	II (Special Controls)
Review Panel:	Radiology

IV. Predicate Device

Identification of Predicate Device:	SpaceOAR System (DEN140030)
Common/Usual Name:	Hydrogel Spacer

V. Device Description

The BioProtect Balloon Implant™ System is composed of a single use, biodegradable, inflatable balloon implant, designed to act as a spacer between the prostate and the rectum. The BioProtect Balloon Implant System is supplied sterile. The balloon is implanted transperineally using transrectal ultrasound (TRUS) guidance and remains stable throughout the radiation treatment and gradually degrades over time.

The BioProtect Balloon Implant System consists of single use components detailed below:

1. Balloon – biodegradable, inflatable balloon acts as a spacer between the prostate and rectal wall.

2. Balloon Deployer – delivery system, the balloon is mounted and folded on the deployer
3. Delivery Kit – an applicator system used to position and deploy the balloon in the intended location. It includes an 18-gauge echogenic needle, blunt-tipped tissue dilator, and balloon introducer sheath.

The BioProtect Balloon Implant System is for prescription use only.

VI. Indications for Use

The BioProtect Balloon Implant System is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space it is the intent of the BioProtect Balloon Implant System to reduce the radiation dose delivered to the anterior rectum.

The BioProtect Balloon Implant System is composed of a balloon made of a biodegradable material that maintains the space for the entire course of prostate radiotherapy treatment and is completely absorbed by the patient's body over time.

VII. Summary of Technological Characteristics Compared to the Predicate Device

The intended use and principles of operation of the BioProtect Balloon Implant System and the SpaceOAR predicate device are identical. Both devices meet the regulatory definition for Absorbable Rectal Spacers outlined in 21 CFR 892.5725.

Both devices facilitate implantation of biodegradable materials in a minimally invasive procedure between the anterior rectal wall and the prostate under transrectal ultrasound (TRUS) guidance using a dedicated delivery system prior to radiotherapy for prostate cancer. Both devices mechanically create a space between the anterior rectal wall and the prostate to protect the anterior rectum from excessive radiation during radiation treatment for prostate cancer. The space created by both devices is performed by injecting fluid at the perirectal layer. Both devices are single-use and are provided sterile to licensed medical professionals only and are biodegradable and absorbed by the body over time. The target population of both devices is adult human males receiving radiation therapy for prostate cancer.

The principal differences between the subject and predicate devices are:

- Material Composition – The BioProtect Balloon Implant is composed of Poly (L-lactide-co-ε-caprolactone) (PLCL) which is a bioresorbable copolymer, whereas the SpaceOAR is comprised of a polyethylene glycol (PEG) hydrogel that is crosslinked *in-situ.*
- Formation of Perirectal Spacing – The BioProtect Balloon Implant is inflated with saline and can be deflated and repositioned if needed, whereas the predicate device is gel formed *in-situ* by mixing two solutions and cannot be repositioned.
- Volume – The inflated balloon contains up to 17 ml of injected saline providing 10-18 mm space height, whereas the predicate device places 10 ml of hydrogel.
- Implantation Process – The BioProtect balloon implant is pre-folded on an integral deployer whereas the predicate is an injectable gel. The implantation procedure of the BioProtect balloon includes establishing a working channel along the plane from the prostate apex to base using a beveled tip dilator dissection with an option of hydro dissection, and then insertion of the balloon through the working channel and slowly filling it with saline. The

inflated balloon is then sealed, using a plug sealing made of the same material as the balloon itself, detached from the deployer and the inflated balloon is left *in situ*.

The SpaceOAR System implantation process consists of preparing the precursor syringe assembling the delivery components for injection, inserting the needle all the way posterior to the prostate base, hydro dissecting the space using saline and then injecting the hydrogel.

- Insertion/Placement – Insertion of the predicate requires hydrodissection that is accomplished by injecting saline via a needle and syringe into the perirectal space. The BioProtect balloon is placed in the desired area on a deployer, following blunt dissection, and is then injected with saline to form a larger pre-shaped balloon.

- Shape – The geometrical shape of the balloon is predetermined whereas the predicate device is injected as a liquid gel, and as such the final shape of the gel is less predictable and can be less symmetrical.

A substantial equivalence table highlighting the similarities and minor differences between the subject and predicate devices is provided below.

Table 1. Substantial Equivalence of the Subject Device as Compared to Predicate Device

Descriptive Information	BioProtect Balloon Implant System (Subject Device)	SpaceOAR System (Predicate Device – DEN140030)
Indications for Use	The BioProtect Balloon Implant System is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space it is the intent of the BioProtect Balloon Implant System to reduce the radiation dose delivered to the anterior rectum. The BioProtect Balloon Implant System is composed of a balloon made of a biodegradable material that maintains the space for the entire course of prostate radiotherapy treatment and is completely absorbed by the patient's body over time.	SpaceOAR System is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space it is the intent of SpaceOAR System to reduce the radiation dose delivered to the anterior rectum. The SpaceOAR System is composed of biodegradable material and maintains space for the entire course of prostate radiotherapy treatment and is completely absorbed by the patient's body over time.
Prescription Use	For prescription use only.	For prescription use only.
Classification and Product Code	21 CFR 892.5725 OVB – Absorbable perirectal spacer	21 CFR 892.5725 OVB – Absorbable perirectal spacer
Mode of Action	System that facilitates implantation of balloon between anterior rectal wall and prostate prior to radiotherapy. This temporarily creates space between the anterior rectal wall and prostate during radiotherapy for prostate cancer which is eventually absorbed following the course of radiotherapy treatment	Systems that facilitate implantation of 10cc PEG biodegradable hydrogel between the anterior rectal wall and prostate prior to radiotherapy. This temporarily creates space between the anterior rectal wall and prostate during radiotherapy for prostate cancer which is eventually absorbed following the course of radiotherapy treatment.
Operating Principles	• Spacer • Implantable • Biodegradable • Biocompatible • Transperineally approach • TRUS guided	• Spacer • Implantable • Biodegradable • Biocompatible • Transperineally approach • TRUS guided

Descriptive Information	BioProtect Balloon Implant System (Subject Device)	SpaceOAR System (Predicate Device – DEN140030)
Material	Poly (L-lactide-co-ε-caprolactone) which is a bioresorbable copolymer	Polyethylene glycol (PEG) hydrogel that is formed in-situ.
System basic components	Biodegradable, injectable balloon (mounted on a deployer) Balloon Delivery Kit (18-gauge echogenic needle, dilator and introducer sheath)	The SpaceOAR® System consists of Components for the preparation of a synthetic, absorbable hydrogel spacer and Delivery mechanism. Once assembled, the Y-connector allows for hydrogel injection via an 18-gauge needle.
Technology	Pre folded Balloon inflated with Saline	When mixed the solutions are cross linked to form a soft hydrogel. The spacer is formed by mixing two solutions, the Precursor, and the Accelerator. The Precursor solution is formed through the mixing of the Diluent solution (Trilysine buffer solution) with the PEG powder. The mixing of the solutions is accomplished as the material passes through a static mixer in the Y-connector prior to passing through an injection needle.
Surgical Approach	Implanted transperineally in a minimally invasive procedure in the space between the prostate and the rectum under transrectal ultrasound (TRUS) guidance using a dedicated delivery system.	Implanted transperineally in a minimally invasive procedure in the space between the prostate and the rectum under transrectal ultrasound (TRUS) guidance using a dedicated delivery system.
Form	Balloon	*In Situ* formed hydrogel
Sizes	In its deployed inflated configuration, the balloon has the following dimensions: Length: 48mm Width: 35mm Height: 10-18mm Height can be controlled depending on desired spacing, by controlling the amount of saline injected prior to balloon sealing.	10 ml injectable gel
Resorption Time	Biodegradable material maintains space for the entire course of prostate radiotherapy treatment (approximately 3 months) and is completely absorbed by the patient's body over time (approximately 6 months).	Biodegradable material maintains space for the entire course of prostate radiotherapy treatment (approximately 3 months) and is completely absorbed by the patient's body over time (approximately 6 months).
Implantation procedure steps	• Establishing a working channel along the plane from prostate base using a beveled tip dilator dissection (Hydro dissection is optional) • Insertion of the balloon through the working channel • filling the Balloon with saline. • Sealing the inflated balloon	• Preparing the precursor syringe • Hydro dissecting the space using saline • Assembling the delivery components for injection, inserting the needle all the way posterior to the prostate base • Injecting the SpaceOAR hydrogel
Sterilization Method	ethylene oxide	ethylene oxide
Sterility	Sterile, SAL 10^{-6}	Sterile, SAL 10^{-6}
Singe Use/ Reuse	Single use only	Single use only
Packaging	Packed in sterile blister and Tyvek located in a humidity bag in a carton box	Packed in sterile blister and Tyvek located in a carton box

The minor technological differences between the BioProtect Balloon Implant System and SpaceOAR System predicate device, raise no new issues of safety or effectiveness. Performance data demonstrate that the BioProtect Balloon Implant System is as safe and effective as the SpaceOAR System. Thus, the BioProtect Balloon Implant System is substantially equivalent to the predicate device.

VIII. Summary of Data to Support Substantial Equivalence

The determination of substantial equivalence was based on an assessment of non-clinical performance data obtained from *in vitro* characterization studies, an *in vivo* animal study, biocompatibility testing of the subject device, and pivotal clinical study.

a. Biocompatibility

Biocompatibility testing of the BioProtect Balloon Implant System was performed per applicable standards on sterilized samples, addressing the following evaluation endpoints:

- Cytotoxicity
- Sensitization
- Irritation/Intracutaneous Reactivity
- Acute Systemic Toxicity
- Material Mediated Pyrogenicity
- Subacute/Sub-chronic Toxicity
- Genotoxicity
- Implantation
- Chronic Toxicity
- Carcinogenicity
- Particulate Analysis

Tests for reproductive and developmental toxicity, toxicokinetics, immunotoxicity and carcinogenicity were determined not applicable to the BioProtect Balloon Implant system since it does not contain any levels of materials considered hazardous, does not contain materials of toxicological significance, and is nonimmunogenic.

Biological risk assessment concluded that all components of the subject device's system, which include the Balloon Implant, Deployer, and Balloon Delivery Kit, are considered safe for their intended use.

b. Bench Testing

Extensive in vitro testing was performed to confirm that the device meets its specifications to address degradation, mechanics, and usability and included:

1. In vitro degradation (physical, chemical, mechanical tests)
2. Effect of radiation dose on the balloon
3. Balloon spacing stability
4. Resistance to internal pressure
5. Usability testing
6. Dimensions verification

Results indicated all acceptance criteria were met.

c. Performance Testing – Animal

In vivo animal studies were performed at various time points (up to 12 months) and included small (rabbit) and large (swine and canine) animal models.

In total, three animal studies were performed. The first (rabbit model) was aimed to assess the safety of the implant, and the other two studies aimed to assess both the safety and performance of the system and implant, including interaction with radiation. Histopathology at one-year post procedure revealed healthy tissue and proper biodegradability of the balloon.

The studies supported the safety, performance, and biodegradability of the BioProtect Balloon Implant System for its intended purpose.

d. Performance Testing – Clinical

A prospective, multi-center, randomized, double-arm, single blind, concurrently controlled study (IDE G17020) was conducted to demonstrate that the subject device's balloon would temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer, and in creating this space, reduce the radiation dose delivered to the anterior rectum. Two hundred twenty-two (222) subjects were enrolled in this clinical study and randomized in a 2:1 ratio to the treatment group (Fiducial markers and Balloon) or Control group (Fiducial markers only). All subjects were diagnosed with T1-T3 prostate cancer, with a planned treatment regime of radiotherapy by means of IMRT.

This study had co-primary endpoints for safety and efficacy. The primary efficacy endpoint was defined as a reduction of at least 25% of the volume of the rectum receiving greater or equal to 70 Gy when compared to pre-implantation values, in 75% of the subjects assigned to the balloon group. The primary safety endpoint was based on the proportion of subjects with Grade 1 or greater rectal adverse events and implantation procedure related adverse events with a duration of at least 2 days through the first six (6) months.

The balloon placement was successful in all balloon group subjects. The primary efficacy endpoint was successfully met with 97.9% of subjects gaining rectal dose reduction >25% in rV70 post-implantation, with a relative mean dose reduction of 84.8% of the volume of the rectum receiving 70Gy. Moreover, the rectal radiation dose was consistently and significantly reduced in all radiation levels (from 40Gy to 80Gy), compared to pre-implantation values, with increasing relative reductions at higher doses. For all, the Sign test p-values were <0.001.

With respect to bladder volume, the pre-implantation mean of 194.3cc (±128.51cc) and post-implantation mean of 231.5cc (±134.56cc) show a modest increase.

Regarding treatment constraint combinations from the study, no plan in the balloon group failed to meet all constraints. There was a significantly higher likelihood in achieving PTV and all rectal constraints (83.5% vs 57.7%) favoring the balloon arm, as well as all PTV and bladder constraints (70.5% vs 60.3%).

The primary safety endpoint was assessed by an independent Clinical Events Committee (CEC) blinded to subject assignment. In this study, the primary safety outcome was successful, and demonstrated that the proportion of subjects with Grade 1 or greater rectal or procedure related adverse events through 6 months was lower in the balloon group compared to the control group. The results revealed a proportion of 18% in the Balloon Group compared to 23.1% in the Control Group, achieving the one-sided non-inferiority test for the Balloon Group ($p < 0.001$). No Serious Adverse Device Event (SADE) or Unanticipated Adverse Device Effect (UADE) occurred during the study.

Balloon stability throughout the radiation treatment course was demonstrated by the stable distance between the rectal wall and the prostate, as measured at last radiation treatment day (1.8 cm) compared to the distance at post implantation (1.9 cm).

Complete balloon degradation at 6 months was demonstrated in 98.5% of the subjects, suggesting that the degradation process over time is safe, and with no potential late complications or side effects due to a partially resorbed balloon.

This study demonstrated the ease of balloon implantation, patient tolerance, and consistent rectal dose reduction. Throughout the entire follow-up period, the balloon group had a lower event rate, suggesting a benefit over time of the balloon compared to the Control. The balloon stability and lack of migration for the entire course of radiotherapy, when combined with the balloon visibility data at 6 months, supports the balloon degradation profile that is maintained throughout IMRT and typically resorbs by 6 months post-implantation.

IX. Conclusion

Based on the clinical performance of the BioProtect Balloon Implant System as documented in the IDE study, the BioProtect Balloon Implant has a safety and effectiveness profile that is similar to the predicate device. In particular, the subject device has the same or similar indications, technological characteristics, and principles of operation as the predicate device. The minor differences between the two devices do not raise any new issues of safety and effectiveness when the device is used as labeled. Therefore, it can be concluded that the BioProtect Balloon Implant System is substantially equivalent to the predicate device.