CLINICAL PROTOCOL

for the

INVESTIGATION

of the

BioProtect Balloon Implant System

Pivotal Study BP-007

Sponsor:

NAME AND ADDRESS

BioProtect, Ltd.
8 Tsor st.
Tzur Yigal
Israel, 4486200

VERSION DATE OCTOBER 07, 2021

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1. NAME AND ADDRESS OF SPONSOR AND REPRESENTATIVES

1.1 STUDY SPONSOR

The Sponsor of this IDE study is BioProtect, Ltd.

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2. IDE PROTOCOL

2.1 PURPOSE OF STUDY

The Balloon Spacer (also called "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 Balloon Spacer to reduce the radiation dose delivered to the anterior rectum. The balloon composed of a biodegradable material that maintains that space for the entire course of prostate radiotherapy treatment and is completely absorbed by the patient's body over time.

This IDE study will demonstrate that the BioProtect Balloon Implant System, when used in prostate cancer patients undergoing radiotherapy by means of IMRT, reduces the radiation dose delivered to the anterior rectum.

2.2 PROTOCOL STUDY CONDUCT

2.2.1 STUDY DESCRIPTION

This study will be a prospective, multi-center, randomized, double-arm, single blind, concurrently controlled study to assess the safety and efficacy of the BioProtect Balloon Implant System in prostate cancer subjects undergoing radiotherapy by means of IMRT. Subjects will be randomized in a 2:1 ratio (balloon implantation:control) to receive either IMRT + marking + balloon implantation or IMRT + marking. The balloon will be inserted during the same session as the marking.

2.2.2 STUDY OBJECTIVES AND HYPOTHESIS

2.2.2.1 OBJECTIVE

The objective of this clinical study is to demonstrate that the balloon, when properly inserted between the prostate and the rectum is safe and effective in reducing the volume of the rectum receiving greater or equal to 70 Gy ($V_{Rectum}70$) by means of IMRT in prostate cancer patients undergoing radiotherapy.

2.2.2.2 PRIMARY EFFECTIVENESS ENDPOINT

The primary effectiveness endpoint will be evaluated in subjects with prostate cancer who are undergoing radiotherapy by means of IMRT and who receive the balloon, with individual patient success defined as a reduction of at least 25% of the volume of the rectum receiving greater or equal to 70 Gy ($V_{Rectum}70$) when compared to pre-implantation values. The study will be considered a success if the rate is significantly greater than 75%; the hypothesis will be evaluated using a one-sided exact binomial test as detailed in **Section 2.3**.

2.2.2.3 PRIMARY SAFETY ENDPOINT

The primary safety endpoint is the rate of occurrence of Grade 1 or greater rectal adverse events and implantation procedure related adverse events with a duration of at least 2 days through 6 months. This rate will be compared between the balloon group and the control group, and the study will be considered a success if statistical significance is achieved on a one-sided non-inferiority test. Details appear in **Section 2.3**.

2.2.3 STUDY POPULATION

Two hundred twenty-two (222) men who meet enrollment criteria will be enrolled at up to 25 sites in the US and outside the US. No more than 40 subjects will be enrolled at an individual center. Subjects will all be male and at least 18 years of age, and will have prostate cancer that is locally confined or extracapsular with no posterior extension (i.e., not involving the rectum) with a planned treatment regime of radiotherapy by means of IMRT. A blocked randomization, with randomly varying block sizes, will be used, to minimize the likelihood that the site will be able to infer the next randomization assignment in the sequence.

All subjects who provide Informed Consent, are randomized and marked or implanted will be included in the intent-to-treat population. It is possible that a subject randomized to the Balloon Group may not be marked or implanted due to an arising health concern or may be excluded intraoperatively due to the inability to perform proper dissection between the prostate and the rectum. Preliminary data will be captured for subjects excluded intraoperatively, documenting the reason(s) for exclusion, and these subjects will be excluded from the primary (Per-Protocol) analyses. These subjects will be included a sensitivity analysis as failures for the balloon group. Additionally, sites will maintain a log of screening failures, documenting the reason for failure. Subjects who are screening failures will be excluded from analysis.

2.2.3.1 INCLUSION CRITERIA

Prospective subjects must meet ***all*** of the inclusion criteria to participate in this clinical study. To be included in the study, the subject must:

- Be at least 18 years of age;
- Have been histologically diagnosed with invasive adenocarcinoma of the prostate, at clinical stage T1-T3 that is locally confined or extracapsular with no posterior extension (i.e., not involving the rectum);
  - The stage of adenocarcinoma will be determined by biopsy. For patients who have very-low or low-risk prostate cancer (i.e., T1c or T2a, Gleason less than or equal to 3+3, and PSA less than 10 ng/mL), the biopsy may be taken up to 9 months prior to screening. For all others, the biopsy must be done no greater than 6 months prior to screening.
  - The presence/absence of posterior extension will be determined by MRI. For patients who have very-low or low-risk prostate cancer (T1c or T2a, Gleason less than or equal to 3+3, and PSA less than 10 ng/mL), the MRI may be taken up to 9 months prior to screening. For all others, the MRI must be taken no greater than 6 months prior to screening.
- Be scheduled for radiation therapy (XRT) for prostate cancer by means of IMRT **and**
- Be willing to adhere to the follow-up schedule and protocol requirements.

2.2.3.2 EXCLUSION CRITERIA

Prospective subjects must **not** meet *any* of the exclusion criteria to participate in this clinical study. These include:

- Pelvic lymph node radiotherapy is planned;
- Any prior invasive malignancy (except non-melanomatous skin cancer) unless the subject has been disease free for a minimum of 5 years;
- Prior radical prostatectomy;
- Prior cryosurgery or radiotherapy for prostate cancer, or other local therapy for prostate cancer;
- Prior radiotherapy to the pelvis, including brachytherapy;
- American Urological Assn. (AUA) Symptom Score $\geq$ 20;
- Active inflammatory bowel disease;
- Known or suspected rectal carcinoma;
- History of prior surgery involving the rectum or anus;
- Venereal warts in the region;
- Prior surgical procedure involving the peri-rectal and/or peri-prostatic area;
- Current urinary tract infection;

- Acute or chronic prostatitis;
- Acute infection requiring intravenous antibiotics at the time of screening;
- Uncontrolled bleeding disorders;
- Unsuitability for anesthesia in the opinion of the anesthesiologist;
- Currently taking anticoagulants or NSAIDS that cannot be stopped for sufficient time prior to the implantation procedure;
- EU citizens may not be enrolled by sites located at any site that is not GDPR compliant;
- Currently incarcerated **or**
- Participation in any other investigational drug, biologic or medical device study within the 30 days prior to the study surgery.

Intra-operative exclusion criteria for the balloon arm subjects only:

- Inability to perform proper dissection between prostate and rectum.

2.2.4 REQUIREMENTS FOR STUDY SITES

- Sites must use IMRT with marking inserted by transperineal approach;
- Sites must follow the contouring instructions, which will be provided separately. These instructions will be used at all participating sites for all enrolled subjects in both arms;
- Sites must perform weekly positioning verification during the XRT;
- Sites must use XRT protocols, where the prescription dose is biologically equivalent to 78-81 Gy in 1.8-2 Gy fractions;
- Sites must perform high resolution CT scans at $\leq$ 2 mm slice thickness **and**
- Sites must export copies of those CTs (axial and sagittal images) in DICOM format to allow for Core Lab analysis of appropriate visits.

2.2.5 STUDY DESIGN

2.2.5.1 OVERALL STUDY DESIGN

This study will be a prospective, multi-center, randomized, double-arm, single blind, concurrently controlled study to assess the safety and efficacy of the BioProtect Balloon Implant System in prostate cancer subjects undergoing radiotherapy by means of IMRT.

Subjects will be randomized in a 2:1 ratio (balloon implantation:control) to receive either IMRT +marking + balloon implantation or IMRT +marking. The balloon will be inserted during the same session of the marking.

Subjects will be blinded to study assignments. It is not practical to blind the surgeon or surgeon's staff since they will participate in the insertion procedure and/or be responsible for

maintaining source documentation. Additionally, the core lab cannot be blinded since the balloon will be visible on the CT images.

All subjects enrolled in the study will be included in an "intent-to-treat" analysis regardless of failure to complete the required follow-up examinations. Subjects will be considered enrolled in the study for the purposes of an intent-to-treat analysis only after they have provided Informed Consent and have been randomized. Preliminary data will be captured for subjects excluded intraoperatively, documenting the reason(s) for exclusion. It is anticipated that very few, if any, subjects will be excluded intraoperatively. Sites will maintain a log of screening failures, documenting the reason for failure. Additionally, subjects who are randomized but not implanted (e.g., due to an adverse event that prevents or significantly delays their radiation treatment) may be removed from the study. Such removals will be documented and reported appropriately. Subjects who are screening failures or who are removed from the study prior to implantation will be excluded from analysis.

This study will utilize a core laboratory for analysis of CT images. Post implantation CT images for the *Balloon Group* will be compared to pre-implantation images to demonstrate the change in distance and potential for rectal protection provided by the balloon.

2.2.5.2 CORE LAB SIMULATIONS

Note that simulations described in this protocol with respect to endpoint determination will be done only by the core lab near the end of the study based on information collected during actual study windows.

2.2.5.3 STUDY DURATION

Each subject will be followed until the last enrolled subject is theoretically due for his 6-month visit, or until follow-up is no longer required for marketing approval, whichever is earlier.

For the purposes of this study, subjects will be evaluated Pre-operatively; at Implantation; Post-implantation; weekly during IMRT Visits (no window); at 6 months post marking/balloon implantation (± 2 weeks) and every 6 months thereafter (± 4 weeks) until the last subject enrolled has completed his 6 month evaluation.

2.2.6 STUDY PROCEDURES

2.2.6.1 INFORMED CONSENT

Only prospective subjects who sign Informed Consent will be allowed to participate in this clinical study. The consent must be provided by the subject. Subjects who do not speak English must be provided a copy of an IRB approved consent in their native language, or (if

the process is approved by the site's IRB) an IRB acceptable translator. The original signed consent will be retained in each subjects study file.

2.2.6.2 VISIT WINDOWS

- Pre-implantation windows vary from 2 to 30 days.
- Post-implantation imaging no sooner than 3 days post implantation and sufficiently prior to planning to allow time for image processing.
- IMRT planning must occur after imaging and no later than 21days post marking.
- IMRT treatments must begin no more than 24 days after marking/ implantation.
- Weekly data recording has no window.
- Follow-up at the 6 months window is ±2 weeks.
- Follow-up for all subsequent visits is ±4 weeks.

2.2.6.3 CTs

CT will be taken for the *Balloon Group* up to 30 days pre-implantation, post-implantation, at the last XRT visit and at the 6-month F/U visit. Additionally, CT may be taken in the Balloon Group at 12 months if remnants of the balloon remain at 6 months.

A CT will be taken in the *Control Group* post-implantation.

Group	Up to 30 Days Pre-Implantation	Post-Implantation	Last X-RT	6 Mo	12 Mo (if needed)
Balloon	X	X	X	X	X
Control		X			

2.2.6.4 PRE-IMPLANTATION EVALUATIONS AND DATA COLLECTION

Data collection will include:

2.2.6.4.1 MRI

MRI to demonstrate that cancer is locally confined or extracapsular with no posterior extension may be taken up to 9 months prior to screening for patients who have very-low or low-risk prostate cancer (T1c or T2a, Gleason less than or equal to 3+3, and PSA less than 10 ng/mL). For all others, the MRI must be taken no greater than 6 months prior to screening.

2.2.6.4.2 Prior to Marking/Balloon Implantation

Within 90 days prior to marking/balloon implantation:

- Medical History and Physical Examination;

- Enrollment of patients meeting all criteria;
- CT scan taken as described in 2.2.4 for the Balloon Group (following randomization);
- Medications currently taken and
- Expanded Prostate Cancer Index (EPIC).

Within 30 days prior to marking/balloon implantation:

- Randomization.

Medical history will include descriptions of prior conditions and treatments, especially if related to the prostate, bladder, rectum, anus or perineal area; and current pain medications and other drug therapies indicated for treatment of prostate cancer.

2.2.6.4.3 Two (2) Days Prior to Marker/Balloon Implantation

- Broad-spectrum antibiotic for 5 days, starting two (2) days prior to marker/balloon implantation (*BOTH Groups*).

2.2.6.5 **BALLOON AND MARKER IMPLANTATION, EVALUATIONS AND DATA COLLECTION**

Prior to the implantation procedure subjects in *BOTH Groups* will receive an enema per center standard for marking the prostate and may receive medication to relieve anxiety. This should be recorded in the medications eData file.

For the *Balloon Group*, urethral catheterization is recommended at the beginning of the implantation procedure to drain the bladder and aid the positioning of the balloon. At the end of the procedure (or per local standards) the catheter should be removed.

The term "Investigator" refers to the radiation oncologist who is in charge of the planning and the IMRT treatments. However, the implantation procedure may be done by the radiation oncologist, or by a urologist who is proficient in performing transperineal procedures via transrectal Ultrasound guidance. Additionally, Investigator performing the simulation may be done by an oncologist, a medical physist, or other qualified person

This protocol requires prostate marking for *all subjects* in both study arms (*Control and Balloon Groups*). Therefore, this visit must be carried out at the location where the marking is usually done by the respective center (OR, Brachytherapy suit, etc.) by the same physician that will be inserting the balloon.

For *both groups*, the marking *MUST* be done transperineally (not transrectally). This technique will avoid potential puncture of the balloon by a marker in the *Balloon Group* and minimize the potential for data bias due to different insertion techniques.

Note: the enema must employ the same protocol for prepping the rectum as would be employed if the marking was being performed transrectally.

The insertion of the balloon will be done using a free-hand approach with the aid of a trans rectal US. Any form of anesthesia may be utilized at the discretion of the implanting physician. However, whenever possible, each center should remain consistent with the choice of anesthesia to avoid potential differences in temporary post-operative sequelae. The subject may receive local, spinal or general anesthesia. However, the subject should be at least relaxed medically to prevent accidental movement.

For Balloon Group subjects, the balloon implantation will be performed after the marking, and will be performed by a urologist/physician who will be trained by the company for balloon insertion.

Also, at the end of the implantation the operator will perform a digital rectal examination (DRE) looking for any irregularities and to exclude any suspicion of injury to the rectum. If the DRE suggests injury, an anuscopy must be used.

For *both study arms*, the implantation visit begins at the time the subject is admitted to the ambulatory setting and continues through discharge from the facility. Implantation evaluations and data collection will include:

- If excluded at this time, reason(s) for exclusion;
- Adverse events as defined by Sections 2.3.6 and 2.3.7 of this Protocol.

2.2.6.6 POST IMPLANTATION IMAGING

Post-implantation imaging must occur no sooner than 3 days post implantation and sufficiently prior to planning to allow time for image processing.

2.2.6.7 IMRT EVALUATIONS AND DATA COLLECTION

2.2.6.7.1 IMRT Simulation and Planning

A CT scan as described in Section 2.2.4 must be done post implantation for **BOTH Groups**. The baseline radiation therapy (XRT) plan, and the core lab simulation, will be based on this CT. Planning must follow the contouring instructions (provided separately). Planning must occur after imaging and no later than 21 days post marking/implantation. The post-implantation simulation will be based on the planning images.

2.2.6.7.2 IMRT Treatments

In general, *for both groups*, IMRT (XRT) must start no more than 24 days after marking/ implantation. Sites will perform a weekly positioning verification using Cone beam or low dose CT scan. For the *Balloon Group*, scan results will also be used to verify balloon spacing of at least 10 mm.

Subjects will receive IMRT based on the sites' dose-fractionation schedule. The following data will be captured for *both groups* during the last day of a weekly visit, for as many weeks as the treatment lasts:

IMRT Data Collection:

This data should be captured once per week on the last day of that weeks' treatment sessions during active IMRT treatment.

Weekly

- For *Balloon Group* – verification of spacing status as at least 10 mm (from prostate to rectum);
- Changes in medications;
- Expanded Prostate Cancer Index (EPIC) assessment (done once at mid-point - assuming the treatment plan exceeds one month (4 weeks));
- Perineal access site healing status (until healed) and
- Adverse events as defined by Sections 2.3.6 and 2.3.7 of this Protocol.

Last XRT Visit

- CT scan taken as described in Section 2.2.4 for the *Balloon*;
- Changes in medications;
- Expanded Prostate Cancer Index (EPIC) assessment and
- Adverse events as defined by Sections 2.3.6 and 2.3.7 of this Protocol.

2.2.6.8 FOLLOW-UP VISITS

The subject will be seen at 6 months (± 2 weeks) and every 6 months thereafter (± 4 weeks) from the time of marking/balloon implantation until the last subject has completed 6 months of follow-up. Data collected will include:

- At the 6 month visit - CT scan taken in the same position as for the IMRT Plan and as described in Section 2.2.4 for the *Balloon Group*;
- Changes in medications;
- Expanded Prostate Cancer Index (EPIC) assessment and
- Adverse events as defined by Sections 2.3.6 and 2.3.7 of this Protocol.

The six (6) month visit will be the last visit conducted for primary analysis.

2.2.7 STUDY COMPLETION, TERMINATION OR LOSS TO FOLLOW-UP

All subjects are expected to remain in the study for at least 6 months following implantation of the balloon. Subjects who complete their 6 month visit prior to the last study subject's completion of the 6 month visit will continue to be followed every 6 months until the last subject enrolled has completed the 6 month evaluation.

Subjects may be withdrawn from a clinical study early due to withdrawal of Informed Consent, loss to follow-up, Investigator medical decision, Regulatory Body decision, an adverse event which would render subsequent data invalid for the purposes of demonstrating the safety and effectiveness of the device, or even death. Any premature termination from the study will be documented, including the primary reason for withdrawal.

2.2.8 DATA COLLECTION SUMMARY

Time Point	Pre-implantation[1]	Implantation	Post-Implantation[4]	IMRT[5] Treatments	IMRT Follow-up
Informed Consent	X[1]				
Medical History & Physical Examination[1]	X[1]				
AUA Symptom Score	X[1]				
Broad Spectrum Antibiotics	X[2]				
Randomization	X[3]				
Medications	X[1]			X	X
CT as per Section 2.2.4 as indicated [6]	X		X	X	X
Perineal Healing Status (until healed)				X	
EPIC Assessment[7]	X			X	X
Adverse Events		As Needed			
Study Completion/ Termination		As Needed			

Study windows:

1. Pre-implantation evaluations.
2. *B*road-spectrum antibiotics must be started 2 days prior to implantation and continued for a total of 5 days.
3. Randomization may occur up to 30 days prior to implantation to allow for facility set up and must occur prior to the pre-implantation CT scan.
4. The Post-implantation period begins at discharge from the facility and extends to the first IMRT treatment.
5. IMRT treatments must start no more than 24 days after marking/ implantation and data will be collect weekly on the last day of that week's visits.
6. CT is taken for the *Balloon Group* up to 30 days pre-implantation and post-implantation, at the last XRT visit and at the 6-month F/U visit. Additionally, CT may be taken in the *Balloon Group* at 12 months if remnants of the balloon remain at 6 months. A CT will be taken in the *Control Group* post-implantation.
7. EPIC is taken at baseline, at mid XRT treatment (assuming the treatment plan is for greater than one month) on last XRT day and at every follow-up visit thereafter.

2.3 STATISTICAL CONSIDERATIONS

2.3.1 GENERAL CONSIDERATIONS

Study data will be made available in listings or electronic files; and study data will be listed by-subject with the randomized treatment indicated. The study results will be summarized using descriptive statistics by randomized treatment. Summaries of baseline information will also include a total column. Standard numeric descriptive statistics include the n (observed values), mean, standard deviation, median, minimum, and maximum values. Categorical data will be summarized with counts and percentages calculated based on the non-missing values. Measures summarized across multiple visits will be summarized by visit and a change from baseline will be provided for numeric variables.

A two-sided p-value of less than or equal to 0.05 and a one-sided p-value of less than or equal to 0.025 will be considered statistically significant unless otherwise specified. A final statistical analysis plan will be completed prior to data analysis.

The homogeneity of the baseline characteristics of the two randomized groups will be evaluated using Fisher's Exact Test, Likelihood Ratio chi-square tests, or Rank-Sum tests.

2.3.2 ANALYSIS POPULATIONS

The intent-to-treat (ITT) population consists of all subjects randomized for the study. The primary analysis population will be based on a Per-Protocol population consisting of ITT in the Control Group and subjects who were randomized to the balloon Group. The ITT population analysis will be included in a sensitivity analysis.

The primary analyses will be completed using a Per-Protocol (PP) Population consisting of subjects who were randomized to and received the balloon device or were randomized to the *Control Group*. It is anticipated that there may be one or two subjects that get randomized to the balloon device, but are not implanted. These subjects will not be included in the PP population or be required to be followed per the protocol. However, the subjects will be included as failures in a sensitivity analysis in the primary analyses for the study.

2.3.3 ADJUSTMENTS FOR MULTIPLICITY

The hypothesis tests for two primary endpoints will be considered independently without adjustment for multiplicity since both tests must reach significance for the study to successfully support the clearance of the balloon device. If both endpoints reach success for the study as outlined below, then three analyses will be performed for consideration in labeling by testing for the superiority of the balloon to the *Control Group*.

- The primary safety endpoint will be evaluated using a two-sided Fisher's Exact test in order to assess superiority of the balloon safety.
- The secondary endpoint rate of Grade 2 or greater rectal adverse events or implantation procedure related adverse events with a duration of at least 5 days will be evaluated using a two-sided Fisher's Exact test.
- The secondary endpoint of the degree of all GU acute toxicity as determined by the Expanded Prostate Cancer Index Composite (EPIC) at the last day of IMRT will be evaluated using a two-sided Rank-Sum (Wilcoxon) test.

The additional endpoints will be evaluated using two-sided tests. If any of these should reach significance at the 0.0167 level, then the results would be considered to be supportive of an additional claim or claims (e.g. a Bonferroni will be used to control for multiplicity).

2.3.4 PRIMARY ENDPOINTS

This study has co-primary endpoints for safety and efficacy.

2.3.4.1 PRIMARY SAFETY ANALYSES

The primary safety endpoint is based on the occurrence of 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 months. Subjects will be counted as having an event if one occurs anytime through Day 197 from the marking date (6 months plus up to 14 days) or as not having an event if they record no events and are followed for at least Day 169 (6 month minus 14 days) from the marking date. A one-sided test of non-inferiority will be completed using the Farrington-Manning method with a non-inferiority bound of 15%. If we denote the s_{pr} to the safety event rate in the *balloon Group* and s_c to be the safety event rate in the *Control Group*, the hypothesis is as follows:

$$H_0: s_{pr} - s_c \geq 0.15 \quad \text{vs} \quad H_1: s_{pr} - s_c < 0.15$$

The study will be a success if the test is significant against a one-sided p-value cut-off of 0.025.

2.3.4.2 SENSITIVITY ANALYSIS

To evaluate the potential impact of missing data, the following sensitivity analyses will be performed: a tipping point analysis performed by imputing the range of combinations of success and failures for the missing subject values in both groups, the comparison will be completed using Kaplan-Meier estimates for the survival rate at 6 months (183 days) following marking, and based on the follow cohort of randomized subjects. In addition, the analysis will be completed using the ITT population and assuming randomized balloon subjects not in the Per-Protocol population are failures.

A logistic model will be used to assess the homogeneity of the study sites and potential interaction between the site and assignment groups with respect to experience of a primary safety event. If the p-value for the interaction is greater than 0.15, then the study sites will be considered suitable for pooling. If the p-value is less than 0.15 then additional analyses of the impact of individual sites will be considered and an estimate of the difference that takes into account the study sites will be provided.

A logistic model will also consider the following factors and their treatment interaction: age greater than or equal to 65 years versus less than 65 years, and race.

For study site and the other covariates, results will be summarized by group and the levels of the covariate.

2.3.4.3 PRIMARY EFFICACY ANALYSES

The primary effectiveness endpoint is assessed only for subjects who receive the balloon device. The primary effectiveness endpoint is a binary assessment of whether a subject obtains at least a 25% reduction in the volume of the rectum receiving greater than or equal to 70 Gy (V_{Rectum} 70). If we denote v_e to be the percentage of subjects meeting the V_{Rectum} 70 success criteria in the balloon arm, the primary hypothesis is as follows:

$$H_0: v_e \leq 75.0\% \text{ vs } H_1: v_e > 75.0\%$$

This analysis will be completed using a one-sided 0.025 exact binomial test with subjects who participate in the primary safety endpoint analysis. The exact 95% CI for the success rate will be provided as well.

Sensitivity analyses will include a tipping point analysis. To assess the validity of pooling the results across the study sites, a Likelihood Ratio chi-square test will be used to assess the homogeneity across the study sites. A p-value of greater than 0.15 will be considered supportive of pooling of the study sites.

Results will also be summarized by age greater than or equal to 65 years versus less than 65 years, and race. A likelihood ratio chi-square test will be used to evaluate the null hypothesis the factors are not associated with outcome.

2.3.4.4 SAMPLE SIZE JUSTIFICATION

The sample size was derived to achieve at least 80% power to meet the study co-primary endpoints (safety and efficacy). For sample size estimation we assume that the co-primary safety and efficacy endpoints are independent. Should positive dependency exist the actual power will be somewhat larger than the calculation presented in this section. Thus, the presented power estimation can be viewed as a lower bound of the actual study power.

The sample of 204 evaluable subjects (68 in Control and 136 in balloon) will provide at least 80% overall power to meet the both study co-primary analyses.

2.3.4.4.1 Primary Effectiveness Endpoint

Assuming that the true response rate in the balloon group is 87.5%, the sample of 136 evaluable subjects will provide at least 95% power to succeed on the primary effectiveness endpoint. The power was estimated using an exact Binomial test with one-sided Alpha = 0.025.

2.3.4.4.2 Primary Safety Endpoint

Assuming that the rate of AEs is 21% and 19% in the Control and balloon, respectively, the proposed sample size yields power of 85% to succeed on the primary safety analysis. The power was estimated using Farrington-Manning test with a non-inferiority margin of 15.0%, and one -sided Alpha = 0.025.

Assuming that the two co-primary endpoints are independent the overall study power is at least 80% (~0.95 0.85).

To account for 8% of drop out rate at 6 months where the primary endpoints are evaluated, the study will enroll 222 subjects (74 in Control and 148 in balloon group, 204/0.92).

It is important to note that the proposed sample size is also sufficient to capture rare / uncommon adverse events. Thus, for example, the proposed sample size for the balloon arm provides 91% chance of observing at least one AE whose prevalence in the intended use population is 1.8%; 87% chance of observing at least one AE whose prevalence in the intended use population is 1.5%; and 75% chance of observing at least one AE whose prevalence in the intended use population is 1.0%.

2.3.4.5 **SECONDARY ENDPOINTS**

Secondary Safety endpoints include:

- The rate of Grade 2 or greater rectal or implantation procedure related adverse events with a duration of at least 5 days and implantation procedure related adverse events in the *Balloon Group* subjects compared to *Control Group* subjects in the 6 month follow-up period post marking and/or balloon implantation.
- Degree of all GU acute toxicity as determined by the Expanded Prostate Cancer Index Composite (EPIC).

The adverse event endpoint will be analyzed using a Fisher's Exact test. The EPIC endpoint will be modeled by visit using a repeated measures model with an unstructured covariance matrix.

Secondary efficacy endpoints include:

- Additional dosimetry parameters ($D_{Rectum}100$, $D_{Rectum}90$, $D_{Rectum}80$, $D_{Rectum}70$) will be evaluated in the balloon arm only, where subjects will serve as their own control (dosimetry reduction after balloon implantation) as the dosimetry parameters are compared to their baseline values per subject.

- Core lab evaluation of distance of rectal wall from the prostate at baseline and last XRT visit. This data will be measured and quantified.

These are all numeric measures and will be compared between groups using Rank-Sum tests.

2.3.5 SAFETY ASSESSMENTS

2.3.5.1 ADVERSE EVENTS

An adverse event is as any clinically significant unfavorable and unintended medical occurrence, including any abnormal sign (e.g., physical exam or laboratory finding), symptom or disease temporally associated with the use of a medical treatment, whether or not it is considered related to the device being studied in a subject. An adverse event may be harmful to a subject taking part in this clinical study or may increase the probability of harm to subjects taking part in the study. An adverse event may be unrelated to the device or procedure needed for implantation, but related to study participation. All clinically significant adverse events must be reported. If an Investigator is unsure about whether to report an occurrence as an adverse event, s/he should contact the study's Clinical Expert.

Adverse event severity will be graded from 1-5, according to the Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.0) as provided by the US Department of Health and Human Services, NIH and the National Cancer Institute.

Adverse Events will be categorized with respect to relationship to the device as not related, possibly related, probably related or definitely related as well at degree of seriousness. To ensure consistency in reporting, the Investigator should use the information below in making the assessment:

Not Related - A temporal relationship to device implantation or with ongoing use of the device, which makes a causal relationship clearly due to extraneous causes, such as other drugs, other devices, chemicals, underlying diseases, environment, etc. The event is clearly not-related to the device implanted or to a function/malfunction.

Possibly Related - Occurring within a reasonable period of time relative to device implantation or with ongoing use of the device, which makes a causal relationship possible, but *plausible explanations **can likely** be attributed to other causes*, such as other drugs, products, chemicals, underlying disease, environment, etc.

Probably Related - Occurring within a reasonable period of time relative to device implantation or with ongoing use of the device, which makes a causal relationship probable where the *plausible explanations **cannot likely** be attributed to other causes*, such as other drugs, products, chemicals, underlying disease, environment, etc.

Definitely Related - Occurring within a reasonable period of time relative to device implantation or with ongoing use of the device, and which *definitely **cannot** be attributed to other causes*, such as other drugs, products, chemicals, underlying disease, environment, etc.

2.3.5.2 UNANTICIPATED ADVERSE DEVICE EFFECTS

2.3.5.2.1 Description

An Unanticipated Adverse Device Effect (UADE) is any serious adverse effect on health or safety or any life threatening problem or death caused by, or associated with, a device, if that effect, problem, or death is not identified in nature, severity, or degree of incidence in this Protocol; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of the subjects.

The number and percent of individual UADEs will be summarized.

2.3.5.2.2 Reporting

Unanticipated Adverse Device Effects must be reported to the Sponsor and to the approving IRB as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.

2.3.6 RISK ANALYSIS

Following is a list of potential adverse events for this study. These include events that have been identified by nature, severity, or frequency in the current literature or in the investigational plan.

2.3.6.1 RISKS

Risks associated with the use of the BioProtect Balloon Implant System in conjunction with the control procedure (marking and IMRT) are expected to be comparable to the risks associated with the control procedure alone. *Risks associated with radiation therapy include:*

- Acute urinary retention (usually related to general anesthesia administration);
- Bladder neck constriction or stricture;
- Fatigue;
- Fragility fractures (if hormone use is added to the treatment);
- Hemospermia (blood in the sperm);
- Hot flashes (if hormone use is added to the treatment);

- Erectile dysfunction;
- Pruritis;
- Radiation cystitis or urethritis;
    - Bladder spasms,
    - Burning with urination,
    - Dysuria (difficulty emptying bladder),
    - Hematuria (blood in the urine),
    - Nocturia (need to urinate during sleeping hours),
    - Urgent, frequent urination.
- Radiation enteritis;
    - Gas,
    - Bowel urgency,
    - Abdominal pain,
    - Abdominal tenderness.
- Rectal-anal mucositis (irritation and ulceration);
- Radiation proctitis and other rectal side-effects;
    - Burning with bowel movements,
    - Diarrhea,
    - Hematochezia (blood in the stool),
    - Hemorrhoids,
    - Loose stools,
    - Rectal bleeding,
    - Rectal fistula,
    - Rectal ulcer,
    - Straining.
- Tenesmus (feeling of incomplete defecation);
- Urinary incontinence;
- UTI;
- Vasovagal episode (usually caused by severe straining).

Risks associated with marking and/or spacer implantation procedure include:

- Fever greater than 100°;
- Site bleeding - mild to moderate;
- Site hematoma - temporary, self terminated;
- Site infection and related symptoms - Infection along the trajectory of the insertion of surgical tools, including the site of implantation;
- Rectal wall puncture.

Risks specifically associated with the BioProtect Balloon Implant Systeminclude:

- Erosion through a hollow organ wall such as bowels, urinary bladder, etc.;
- Incomplete absorption;
- Inflammatory reaction;
- Migration of the device from the desired location;

- Needle penetration into bloodstream, bladder, prostate, rectal wall, rectum or urethra;
- Premature balloon deflation;
- Prolonged or delayed procedure;
- Rectal perforation;
- Tissue necrosis.

2.3.6.2 MINIMIZATION OF RISKS

Adequate measures have been taken to minimize all of the above risks prior to initiation of a U.S. pivotal clinical study, including proper design specification and review, preclinical testing, and clinical evaluations within and outside the United States.

BioProtect will provide appropriate training to each investigator prior to each site's respective study initiation. Investigators will be trained on the technique, selection criteria, and protocol for the clinical study prior to their first implantation procedure. The training will address topics such as the indications and contraindications for the use of the device, the implantation procedure, the study contouring and dosing calculations, follow-up care and management of adverse events.

The initial balloon implantations will be done with the supervision of a BioProtect representative and after a methodic training conducted by BioProtect. The number of procedures proctored will be at least one per implanting physician. Each site will be notified when the Sponsor is satisfied that a Sponsor representative presence is no longer required.

Training will include thorough reading of the IFU, an in vitro demonstration, thorough review of the training video presenting a full procedure on a human case and doing a procedure under the supervision of a Proctor.

Investigators will assess the possible presence of the risks associated with the balloon implant during the implantation procedure, and at each IMRT/follow-up visit by physical and/or radiologic examination and subject interview as applicable.

BioProtect will train and assign monitors to verify that appropriate data is recorded for all study subjects for whom Informed Consent is obtained; and that no study procedures are administered without Informed Consent. A core lab will review radiographic films/digital files to ensure a non-biased evaluation of radiographic endpoints. BioProtect will appoint a qualified radiation oncologist to evaluate potential safety issues and to oversee and review medical monitoring issues. Additionally, a CEC will be appointed to evaluate and adjudicate adverse event data prior to submission of the marketing application.

2.3.7 RATIONALE FOR THE INVESTIGATION

Although there are risks associated with this implantation, they are expected to be infrequent. Only one serious event related to the device has been observed in the prior feasibility study in

Israel. The balloon was over inflated to a height of over 30 mm (instead of 15-18 mm). When digital rectal examination was done, the operator noticed that the rectal wall was too tight and was cracked. To avoid future ischemia, the balloon was punctured and the balloon was removed transrectally. The rectum was sutured and the subject was treated with antibiotics and monitored for 3 days in the hospital with mild to moderate discomfort in the anus and perineal area. No additional effects were observed. This event was reported as a serious event to relevant authorities.

Following this incident, BioProtect reviewed the cause for the incident as a combination of issues: (1) rectal adhesions that prevent the rectum from expanding laterally; (2) rapid inflation (less than 10 seconds); (3) increase height of the balloon (30 mm) and large volume (27 ml) and (4) pressure applied on the rectum during the balloon inflation from the TRUS probe.

This event occurred in January 2009 and has not occurred since.

The BioProtect Balloon Implant Systemis a device developed to assist the radiation-oncologist in the treatment of prostate cancer that is locally confined or extracapsular with no posterior extension (i.e., not involving the rectum). It is implanted with the same transperineal approach used in brachytherapy, with the use of TRUS guidance throughout the entire procedure, and is performed with local anesthesia and light sedation. The procedure takes only several minutes.

There are three well documented correlations that comprise this risk: benefit ratio analysis:

1. The higher dosage of radiation to the prostate, the better survival rate and lesser tumor recurrence rate (**Attachment to this protocol** - 1, 2, 3, 4).
2. The higher dosage of radiation to the rectum, the higher rate of acute and late and chronic grade 2 and 3 rectal toxicity (**Attachment** to this protocol - 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22). In most cases, this is in correlation with the dosage to the prostate.
3. The chances for late and chronic grade 2 and 3 rectal toxicity are very high in patients experiencing acute grade 2 and 3 rectal toxicity. (**Attachment to this protocol** - 7, 16).

While it is advantageous to treat prostate cancer with the highest feasible dose, it is currently avoided by most therapy centers due to the fact that higher dosage to the prostate will eventually result in higher dosage to the rectum. Inserting the balloon in situ between the prostate and the rectum will enable admission of higher dosage whether as total (accumulative) or per session (hypofractionation) or both, potentially reducing acute and late and chronic rectal toxicity.

The rectal toxicity of conventional radiation therapy (XRT) and even the current focused XRT machinery and methods (3D- CRT, IMRT and IGRT), and the hypofractionation trend, potentially can be reduced as lesser radiation at any given dose to the prostate will eventually reach the rectum. Grade 2-3 late and chronic toxicity ranges from 5 to 20 % and more (in particular with hypofractionation). The adverse event rate (Grade 1 events) for the Augmenix SpaceOAR was 34% (DEN140030).

The potential reduction of radiation to the rectum at any given radiation dose to the prostate will potentially reduce acute rectal toxicity, which in turn may reduce the late and chronic rectal toxicity.

The assumed potential risk of using the BioProtect Balloon Implant Systemis mainly the potential risk for rectal perforation and from injury during the implantation procedure. It should be noted however, that unlike the late complications associated with high-dose radiation that are chronic and may take years for resolution, this potential risk is temporary and reversible. Nevertheless, the potential risk of rectal perforation is mitigated by the following actions:

1. The entire procedure will be done with the guidance of Trans Rectal Ultra Sound (TRUS); and the user will be a well-trained urologist or physician that is familiar with the brachytherapy transperineal approach using TRUS.
2. The user will be well trained by the company to the specific implantation procedure with relation to the anatomy. This will be done by thorough reading of the IFU, simulating the implantation on a phantom model using TRUS, explanation of videos showing the phantom simulation and human real case simulation, and supervising the initial cases as needed, by a company trained physician.
3. The delivery system uses a spinal needle type, which is blunt at the tip.
4. The user will instructed to palpate the rectum before inflating the balloon, to reveal any potential perforation that may be missed by the TRUS, and if deemed necessary, to use an anuscope to demonstrate intact rectal epithelium.

Other potential risks that may be associated with the use of the device are commonly known side effects associated in such transperineal approach procedure (prostate biopsy, brachytherapy etc.) and are listed in Section 2.3.6.1 of this Protocol.

Additionally, FDA recently approved the SpaceOAR Hydrogel (DEN 140030) as an “absorbable perirectal spacer”. The approved indication for SpaceOAR is 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.

The BioProtect Balloon Implant Systeme indication is similar to the cleared SpaceOAR device. The BioProtect Balloon Implant Systemis 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 balloon to reduce the radiation dose delivered to the anterior rectum. The balloon composed of biodegradable material that maintains that space for the entire course of prostate radiotherapy treatment and is completely absorbed by the patient's body over time. There is also the advantage that the balloon can just be deflated with a needle stick if the placement isn't satisfactory.

Based on the above correlation statements, and based on the potential benefit and risk claims above, BioProtect believes that the potential benefit for the patients is higher than the potential risk.

2.3.8 STUDY RESULTS

There will be no interim analysis during the clinical study. BioProtect plans to prepare a multicenter publication following the unblinding of the data at study completion. Regardless of the study results, BioProtect will submit the results for publication in the scientific literature and, if appropriate, will present these results at professional meetings. Results will also be posted on clinicaltrials.gov and the scientific article will be available via the company website. BioProtect anticipates submission of the publication within 24 months of study completion.

2.4 DEVICE DESCRIPTION

The balloon is a biodegradable balloon system indicated to temporarily position the anterior rectal wall away from the prostate thereby reducing the radiation dose delivered to the anterior rectum in patients undergoing IMRT for the treatment of prostate cancer. The balloon e is made of Poly (L-lactide-co-ε-caprolactone), commercial name RESOMER® LC 703 S, manufactured by Evonik Industries AG, GmbH.

The system is comprised of: an echogenic needle, which is inserted while injecting saline slowly to facilitate the dissection of the plane between the prostate and rectum; a single use, biodegradable, pre-folded, inflatable balloon; and an internal stainless steel inflation tube which is attached to the balloon (balloon deployer) within a stainless steel retaining tube with a PTFE outer sheath.

The balloon is folded inside the outer sheath and a balloon plug is attached to the tip of the internal inflation tube. The tube allows for the insertion and inflation of the balloon, and sealing of the balloon by the plug attached to its tip. The balloon is inflated slowly with saline (16-17 ml), sealed, and the deployer is then removed, leaving the inflated balloon in situ. The balloon deployer is for single use only.

The BioProtect Balloon Implant Systemis supplied sterile and for one time use. The balloon is implanted transperineally using TRUS guidance.

Once inserted, the inflated balloon gradually hydrolyzes and is fully degraded at 12 months post implantation based on low absorption CT. The products of biodegradation are absorbed and cleared via respiration and renal filtration.

2.5 STUDY MONITORING

Clinical sites will be monitored periodically to ensure concordance with FDA regulations, the validity and integrity of the data and the safety of the study subjects.

2.5.1 MONITORING ORGANIZATION

Study monitoring functions will be performed, in compliance with recognized Good Clinical Practices as applied to medical device studies, FDA's IDE guidance documents, and as outlined in 21 C.F.R. § 812.43(d) and 21 C.F.R. §812.46. BioProtect will maintain responsibility for monitoring this Clinical Study.

In addition to ensuring adequate communication between the Investigators and the study Sponsor, the monitor's duties include on-site visits and review of study documents and results. Monitors will be provided with appropriate training regarding the device under investigation and will operate under written procedures to ensure compliance with the protocol.

2.5.2 ON SITE MONITORING

On-site monitoring visits include a pre-study visit, periodic visits, and a close-out visit at the end of the site’s participation in the study. The pre-study visit is intended to provide an opportunity for the monitor to review the Investigational Plan with the Investigator and to ensure that the Investigator:

- Has appropriate training, facilities, subject load, time and willingness to comply with study requirements;
- Has the approval of the supervising Institutional Review Board (IRB);

- Has all study documentation and required records on site and
- Assumes responsibility for the investigation at her/his center.

Periodic visits are intended to assess adherence to the Investigational Plan, maintenance of Records and Reports, accountability of investigational devices; and provides for review of source documents for accuracy, completeness, and legibility. During these periodic visits, the monitor is required to assess the progress of the study toward meeting study objectives; to identify any concerns that stem from observations of device performance and/or review of the subject records, study management documents or Informed Consent documents; to ensure that the site has assessed adverse events according to protocol requirements; and to ensure accountability of all subjects that have been treated under the study.

The monitor's final on-site visit at completion of the study is intended to ensure that all the data have been properly completed and to have a closing meeting with the Investigator and his/her staff members to discuss findings, observed problems and potential solutions.

Reports of the on-site visits will be made by the monitor and will include a means of tracking resolution of concerns, completion of appropriate follow-up activities, completion of assigned tasks, and any necessary corrective actions. At the close of the study, a final report will be prepared by the monitor for each site.

2.5.3 DATA COLLECTION

BioProtect will verify that appropriate data is recorded for all study subjects for whom Informed Consent is obtained; and that no study procedures are administered without Informed Consent. This study will utilize electronic data capture where possible. Documentation will be provided for study subjects who choose to terminate study participation and for subjects terminated by their physicians. A full explanation of the reasons for non-participation will be provided.

Data will be reviewed to identify inconsistent or missing data and Unanticipated Adverse Device Effects. Data problems will be addressed in calls to the investigational sites and during site visits. All hard copy forms and data files will be secured to ensure confidentiality. Quality assurance procedures are designed to ensure that complete, accurate and timely data are submitted, that protocol requirements are followed, and that adverse events are reported as required under Section 2.3.6 and Section 2.3.7 of this protocol.

2.5.4 INITIAL DEVICE IMPLANTATIONS

If a site did not take part in a previous study or has not been previously trained on the insertion technique, the initial balloon implantations will be done with the supervision of a BioProtect representative and after a methodic training conducted by the Company. Training will include thorough reading of the IFU, and may include activation of a demo system, full

simulation on a phantom, analyzing videos showing phantom simulation and a human case. Retraining, if deemed necessary for sites that took part in the previous study will be provided.

A Sponsor representative also will attend initial device implantations, as needed, to provide assistance with study management training, including compliance with specific record keeping and reporting requirements. A data review with the Investigator by the study monitor will be held after a few initial implantations to assure adherence to the study protocol and to provide guidance to avoid continuing problems with study procedures and data collection.

2.5.5 REVIEW OF STUDY DOCUMENTS

The monitor will review completed data forms and study documentation for accuracy, completeness, and protocol compliance. The following documents will be audited:

- The Clinical Trial (Investigator) Agreement signed by the Investigator, indicating his/her agreement to participate in the investigation and willingness to comply with all study requirements.
- Data Collection Reports will be reviewed for errors, omissions, internal consistency, and signature and dates in the appropriate sections. The monitor will assume responsibility for any follow-up activities that result from review of these visits. Subject Informed Consent documents will be reviewed for completeness.
- Study Monitor Reports, including pre-study visits, initial implant visits, on-site visits or final visit reports, submitted by a site monitor will be reviewed by a senior monitor. The monitor will assume responsibility for any corrective action.

2.5.6 MEDICAL MONITORING

The Sponsor will appoint a qualified radiation oncologist to oversee all medical monitoring issues. Duties of the Clinical Expert include, but are not limited to:

- Review of adverse events which are categorized as serious/severe, whether or not device related;
- Review of all device related adverse events;
- Review of adverse events which exceed the anticipated rates of occurrence;
- Review of any possible or definite UADEs;
- Review of all deaths;
- Review of the clinical sections of the FDA submission at study completion;

- Being available to the CEC and FDA for medically related questions regarding this clinical study.

2.5.7 CEC

BioProtect will engage a Clinical Events Committee (CEC) to review and adjudicate data for all adverse events prior to the submission of the marketing application.

2.5.8 Disposition of Study Devices and Data

All investigational devices received and used by the Investigator will be inventoried and accounted for throughout the study. The BioProtect Balloon Implant System will be stored in a secure area with restricted access, separate from other medical devices. When instructed by the study Sponsor, the Investigator will return any remaining devices, accompanied by a Device Return Form supplied by the study Sponsor. The Investigator will not supply investigational devices to any person except those designated by him/her as co-Investigators. If a balloon is explanted from a subject for any reason, it must be returned to BioProtect following the instructions provided by BioProtect.

All information received by BioProtect pertaining to subjects will be held on a confidential basis. This information may be subject to audit by regulatory authorities where appropriate. Authorized agents of BioProtect will have the right to inspect and copy information in subject files. Where possible, copies will be blinded to replace subject identifying information with subject identifiers.

2.6 Labeling

The surgical video, training materials, Instructions for Use, and all implants and accessories used for implantation will be labeled according to federal regulations (21CFR 812.5) including the following statement, "**CAUTION – Investigational Device. Limited by United States Law to Investigational Use**."

2.7 Informed Consent

Suitable candidates will be informed about the nature of the study and the possible risks involved, and will be provided the opportunity to sign Informed Consent. The prospective subject will be able to ask questions of the Investigator, and will be allowed to review the consent form at his leisure. Since the insertion of the balloon during radiotherapy is elective surgery, this discussion may be held days or weeks prior to any study surgery. The Investigator or the study coordinator, as appropriate, may answer additional questions the subject may have at an additional office visit or by telephone. Due to the extended time of the consent process, it is possible that the subject will sign the consent at home, and so the date of signature of the Investigator (if Investigator signature is required by IRB) may be different from the date of the subject's signature.

Only prospective subjects who sign Informed Consent will be allowed to participate in this clinical study. The consent must be provided by the subject. Subjects who do not speak English will be provided a copy of an IRB approved consent in their native language, or (if the process is approved by the site's IRB) an IRB acceptable translator.

The original of the sites IRB approved Informed Consent template will be kept in the site's study files. Each site will provide the study Sponsor with a copy of the IRB approved and stamped Informed Consent template. The original signed consent will be retained in each subjects study file.

Attachment

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