Statistical Analysis Plan

Investigation of the ProSpace™ Balloon Spacer
Pivotal Study BP-007
SAP Version 2

BioProtect, Ltd., BP-007

Prepared by

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Statistical Analysis Plan

Approval

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1 Abbreviations

AE	Adverse Event
CEC	Clinical Events Committee
CI	Confidence Interval
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
EPIC	Expanded Prostate Cancer Index Composite
FDA	US Food and Drug Administration
GU	Genitourinary
HHS	US Department of Health and Human Services
IDE	Investigational Device Exemption
IMRT	Intensity Modulated Radiation Therapy
ITT	Intent to Treat
NIH	National Institutes of Health
OUS	Outside US
PP	Per-Protocol
SAS®	Statistical Analysis Software®
US	United States
XRT	Radiation Therapy

2 Applicable Documents

The following documents are relevant to the BioProtect BP-007 analysis plan:

- Clinical Study Protocol BP-007
- Study contouring instructions

3 Introduction

3.1 Background

The ProSpace Balloon Spacer (also called “ProSpace™ System” “BioProtect Balloon Implant™ System”, “ProSpace™ Balloon System”, “ProSpace™ Balloon” and “BioProtect SpaceGuard™ 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 ProSpace System to reduce the radiation dose delivered to the anterior rectum. ProSpace is a 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 is a prospective, multi-center, randomized, double-arm, single blind, concurrently controlled study to assess the safety and efficacy of the ProSpace Balloon in prostate cancer subjects undergoing radiotherapy by means of intensity modulated radiation therapy (IMRT).

The study has co-primary endpoints for safety and efficacy. The primary safety endpoint is the rate of Grade 1 or greater rectal adverse eventslasting at least 2 days through the first 183 days (six months) that

are device-related or marking/implantation procedure-related. This rate will be compared between the ProSpace group and the control group with a non-inferiority assessment. The adverse events qualifying as primary safety events will be determined through adjudication by a Clinical Events Committee (CEC). The primary efficacy 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).

3.2 Changes to Planned Analyses

Review of the statistical analysis plan identified that windowing is not required to capture events in the first 6 months since the events are classified based on the onset date. Hence, the primary safety analysis would be more accurate if based on events through Day 183 (6 months). The primary safety analysis was updated to reflect this change and the protocol specified cut-off based on 197 days was moved to be a sensitivity analysis. The following changes are reflected in the SAP:

- Section 10.3.4.1.1 now states that the primary safety analysis will include events from marking through Day 183 (6 months). Section 10.3.4.1.3 has been updated to include a sensitivity analysis for the primary safety endpoint from marking through Day 197.

- It has also been clarified in Section 10.3.4.1.3 that the sensitivity analysis using the Kaplan-Meier method will provide estimates for the proportion of subjects experiencing AEs of interest through Day 183.

In addition, Section 10.3.4.1.1 now describes how the primary safety endpoint will be determined through CEC adjudication and clarifies that events related to anesthesia or to the use of a foley catheter will not be considered marking or implantation procedure-related.

It has been clarified in Section 10.3.5.1 that the secondary EPIC safety endpoint will be evaluated for four domains: Urinary Incontinence, Urinary Irritative, Bowel, and Sexual.

Section 10.3.5.2 clarified that the Sign-Rank test would be used for a within-group paired difference comparison.

4 Study Objective

The objective of this clinical study is to demonstrate that the ProSpace 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.

5 Investigational Plan and Study Design

This study is a prospective, multi-center, randomized, double-arm, single blind, concurrently controlled study of the ProSpace Balloon 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 + ProSpace implantation or IMRT + marking. Subjects in the Balloon Implantation Group (*ProSpace Group*) will have the ProSpace Balloon inserted during the same session as the marking.

Subjects will be evaluated Pre-operatively; at marking/implantation; Post-marking/implantation; weekly during IMRT Visits (no window); at 6 months post marking/implantation (± 2 weeks); and every 6 months thereafter (± 4 weeks) until the last subject enrolled is due for his 6-month evaluation. There will be no interim analysis performed during the clinical study.

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

for the *ProSpace Group* up to 30 days pre-implantation, post-implantation, at the last XRT visit, and at the 6-month follow-up visit. CT may also be taken in the *ProSpace Group* at 12 months if remnants of the balloon remain at 6 months.

Two hundred twenty-two (222) men will be enrolled at up to 25 sites in the US and outside the US, with no more than 40 subjects enrolled per site. 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.

Subjects will be blinded to study assignments. The surgeon, surgeon's staff, and core lab cannot be blinded due to the nature of the marking/implantation procedure and device.

This study has co-primary endpoints for safety and efficacy. The primary safety endpoint is the rate of Grade 1 or greater rectal adverse events lasting at least 2 days through the first 183 days (six months) that are device-related or marking/implantation procedure-related. The primary efficacy endpoint will be evaluated with a one-sided test of non-inferiority using the Farrington-Manning method with a non-inferiority bound of 15%. If s_{pr} denotes the safety event rate in the *ProSpace Group* and s_c denotes the safety event rate in the *Control Group*, the primary safety hypothesis is as follows:

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

The primary efficacy endpoint is a binary assessment of whether a subject obtains at least a 25% reduction at 21 days post-implantation in the volume of the rectum receiving greater than or equal to 70 Gy (V_{Rectum} 70). The primary efficacy endpoint will be assessed only for subjects who are randomized to the ProSpace Group and receive the ProSpace device, and it will be evaluated using a one-sided 0.025 exact binomial test. If we denote v_e to be the percentage of subjects meeting the V_{Rectum} 70 success criteria in the *ProSpace Group*, the primary hypothesis is as follows:

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

The hypothesis tests for the two co-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 ProSpace device. The study will be successful if both the primary safety endpoint and primary efficacy endpoint both reach statistical significance in the tests outlined above against one-sided p-value cut-offs of 0.025.

6 Sample Size Justification

The sample size of 222 (74 in the *Control Group* and 148 in the *ProSpace Group*) was derived to achieve at least 80% power to meet the study co-primary endpoints (safety and efficacy) and to allow for an 8% drop-out rate at 6 months where the primary endpoints are evaluated. A sample of 204 evaluable subjects (68 in the *Control Group* and 136 in the *ProSpace Group*) will provide at least 80% overall power to meet both study co-primary analyses.

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.

For the primary safety endpoint, assuming that the rate of AEs is 21% and 19% in the *Control* and *ProSpace Groups*, 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 of 0.025. Additionally, the events used for the safety analysis will have been adjudicated by a CEC and the outcome of that adjudication will be used for the purpose of this analysis.

For the primary efficacy endpoint, assuming the true response rate in the *ProSpace Group* is 87.5%, the sample of 136 evaluable subjects will provide at least 95% power to succeed on the primary effectiveness analysis based on a one-sided 0.025 exact binomial test.

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

The proposed sample size is also sufficient to capture rare / uncommon adverse events. For example, the proposed sample size for the ProSpace 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%.

7 Visit Schedule and Visit Windows

Data collection will occur according to the following guidelines and as detailed in Table 1 below.

Screening

Within 90 days prior to marking/implantation:

- Medical History and Physical Examination;
- Enrollment of patients meeting all criteria;
- Medications currently taken;
- Expanded Prostate Cancer Index (EPIC).

Post Screening and within 30 days prior to marking/implantation:

- Randomization;
- CT scan for the *ProSpace Group* (following randomization).

Post-marking/implantation:

- Post-marking/implantation imaging must occur between 3 and 21 days post marking/implantation.
- IMRT planning must occur after imaging, but no later than 21 days after marking/implantation.
- 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.

7.1 Table 1. Data Collection Summary

Time Point	Pre-implantation[1]	Implantation	Post-Implantation[4]	IMRT Treatments[5]	IMRT Follow-up[9]
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 [6]	X[1]			X	X
CT[7]	X		X	X	X
Perineal Healing Status (until healed) [6]				X	
EPIC Assessment [8]	X			X	X
Adverse Events		As Needed			
Study Completion/ Termination		As Needed			

Study windows:

1. Pre-implantation evaluations.
2. Broad-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 collected weekly on the last day of that week's visits.
6. Medications, perineal healing status (until healed), and verification of spacing status (*ProSpace Group*) are captured once per week during active IMRT treatment on the last day of that week's treatment sessions.
7. CT will be taken for the *ProSpace Group* up to 30 days pre-implantation and post-implantation, at the last XRT visit and at the 6-month follow-up visit. Additionally, CT may be taken in the *ProSpace Group* at 12 months if remnants of the balloon remain at 6 months. CT will be taken in the *Control Group* post-implantation.
8. EPIC will be 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.
9. The subject will be seen at 6 months (± 2 weeks) and every 6 months thereafter (± 4 weeks) from the time of marking/implantation until the last subject has completed 6 months of follow-up.

8 Study Populations

Subjects will all be male, 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.

9 Analysis Populations

The analysis populations are defined in compliance with E9 guidance from the ICH: Statistical principles for clinical trials[1].

Intent-to-Treat (ITT) Population

Intent-to-Treat (ITT) population will include all randomized subjects, regardless of whether they underwent a surgery or not. All subjects in the ITT population will be analyzed as members of the group to which they were assigned irrespective of actual treatment received.

The ITT population will be used for a sensitivity analysis for the study co-primary endpoints.

Per-Protocol (PP) Population

The Per-protocol (PP) population is a subset of the ITT population, and will include:

- All subjects randomized to the Control group.
- *ProSpace* group subjects who were marked and implanted as planned.

The PP population will be used for analyses of the study's primary and secondary endpoints (efficacy and safety).

A listing of all protocol deviations will be evaluated prior to the database lock by the study's medical monitor (clinical expert).

10 Statistical Methods

10.1 General Statistical 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 (including the 95% confidence interval), standard deviation, median, minimum, and maximum values. Categorical data will be summarized with counts and percentages calculated based on 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 or a one-sided p-value of less than or equal to 0.025 will be considered statistically significant unless otherwise specified.

All statistical analyses and summaries will be generated using SAS version 9.4.[2]

[1] HHS, FDA (1998). *Guidance for industry: E9 Statistical Principles for Clinical Trials*

[2] SAS software. Version 9.4. Copyright © 2016 SAS Institute Inc., Cary, NC, USA.

Handling of Missing Data

The handling of missing data from the primary safety and efficacy analyses is addressed through the sensitivity analyses identified in Sections 10.3.4.1.3 and 10.3.4.2.3. All other summaries will be based on available data, without imputation of missing data.

10.2 Adjustments for Multiplicity of Endpoints

The study has two co-primary endpoints. Each co-primary endpoint will be tested using one-sided alpha equal to 0.025 tests. To control the overall type I error, both co-primary hypotheses must be met to declare success on the primary analysis.

If both co-primary endpoints reach success for the study, then the following three secondary analyses will be performed for consideration in labeling by testing for the superiority of ProSpace to the control:

- The primary safety endpoint will be evaluated using a two-sided Fisher's Exact test in order to assess superiority of ProSpace safety.
- The secondary endpoint rate of Grade 2 or greater rectal adverse events that are also device-related, marking/implantation procedure-related, or IMRT-related with a duration of at least 5 days will be evaluated using a two-sided Fisher's Exact test.

The additional endpoints will be evaluated using two-sided tests. The secondary analyses will control for multiplicity to maintain an overall Type I error rate of 0.05. If any of these should reach significance at the 0.0167 level, then the results would be considered supportive of an additional claim or claims (i.e., a Bonferroni will be used to control for multiplicity).

10.3 Evaluations and Statistical Analyses

10.3.1 Subject Disposition

Subject disposition will include the total number of subjects screened and number of screen failures recorded in the database, which will include any patient who consented to participate whether they failed eligibility or withdrew prior to marking.

Subject follow-up will be summarized by treatment arm at baseline, marking/implantation, post-implantation, 6 months and every 6 months thereafter during the study. For each period, expected follow-up will be calculated as the number of subjects theoretically reaching that period, minus the number of subjects not yet overdue for that visit and minus any deaths occurring since the last visit. Actual follow-up for each period will be summarized by frequency and the percentage of expected follow-up. The frequency and percentage of subjects missing a visit window and/or discontinuing the study will be included, along with the reasons for discontinuation.

Study enrollment by location (US and outside US) and by each site will be summarized by the number and percentage of subjects.

10.3.2 Demographics and Baseline Characteristics

Demographic and baseline information will be summarized for the PP population using descriptive statistics. Categorical variables (gender, race, clinical stage at baseline) will be summarized using frequency and percentages. Numeric variables (age, height, weight, BMI, AUA Symptom Score at baseline) will be summarized using descriptive statistics as total number of subjects surveyed (N), mean, median, standard deviation, minimum, maximum, and inter-quartile range.

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.

Medical history will be listed and will include descriptions of prior conditions and treatments, especially if related to the prostate, bladder, rectum, anus, or perineal area; and current medications and other drug

therapies indicated for treatment of prostate cancer. The overall number and percentage of subjects with one or more medical history findings by type will be summarized.

10.3.3 Procedure Information

Procedure information will be summarized for the per protocol population.

Descriptive statistics in the form of frequencies and percentages will be provided related to the marking/implantation procedures, including the method of marking, ease of marking, dissection method, ProSpace positioning success, ease of instrumentation use, ease of implantation, and problems revealed by digital rectal exam (DRE).

10.3.4 Co-Primary Endpoints and Analyses

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

10.3.4.1 Co-Primary Safety Endpoint and Analysis

10.3.4.1.1 Primary Safety Endpoint

The adverse events qualifying as primary safety events will be determined through adjudication by the CEC. The primary safety endpoint is based on the occurrence of one or more adverse event as follows, as indicated on the CEC CRF:

- Event is indicated to be a Grade 1 or greater rectal event lasting at least 2 days through the first 183 days (6 months) and
- Event meets one of the relatedness classifications:
    - Event is indicated to possible, probably, or definitely device-related;
    - Event is related to marking or
    - Event is related to the balloon implantation procedure.

Note that events related to anesthesia or to the use of a foley catheter will not be considered marking or implantation procedure-related.

Subjects will be counted as having an event if one occurs anytime through Day 183 (6 months) from the marking date or as not having an event if they record no events and are followed through at least Day 169 (6 month minus 14 days) from the marking date. Subjects who terminate the study before Day 169 and did not experience the AE of interest will be considered missing from the PP population and not included in the primary safety analysis. The impact of these subjects will be evaluated in a sensitivity analysis for the primary safety endpoint as described below.

10.3.4.1.2 Primary Safety Analysis

The primary safety analysis will be done using the PP population.

The analysis of the primary safety endpoint will entail a one-sided test of non-inferiority using the Farrington-Manning method with a non-inferiority bound of 15%. If we denote s_{pr} to be the safety event rate in the *ProSpace Group* and s_c to be the safety event rate in the *Control Group*, the primary safety hypothesis is as follows:

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

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

The SAS code for analyzing the primary safety endpoint is as follows:

```
PROC FREQ ;
      TABLES TRTPN*GRADE1 / RISKDIFF (NONINF MARGIN=0.15 METHOD=FM) ;
      RUN ;
```

where TRTPN is the treatment group and GRADE1 is a binary variable indicating whether a subject experienced a primary safety event (1 = event, 0 = no event).

10.3.4.1.3 Sensitivity Analysis for Primary Safety Endpoint

The analysis of the primary safety endpoint will be repeated as a sensitivity analysis using the period from marking through Day 197 (6 months plus 14 days).

To evaluate the potential impact of missing data on the primary safety endpoint, the following sensitivity analyses will be performed using the ITT population: A tipping point analysis will be performed by imputing the range of possible combinations of successes and failures for the missing subject values in both groups, ranging from all failures to all successes. For every imputation combination across the two groups, the effect on the primary safety hypothesis will be reported to evaluate the robustness of the analysis to patterns of missing data across the two groups. The tipping point analysis will be performed using the ITT population.

In addition, to evaluate the robustness of the safety outcome, Kaplan-Meier estimates of time to Primary Safety AE will be provided. Based on the Kaplan-Meier curves, estimates for the proportion of subjects experiencing AEs of interest, along with the 95% confidence interval for the difference between the groups, will be provided at 183 days (6 months) from the marking date.

10.3.4.1.4 Poolability Analysis for Primary Safety Endpoint

Poolability analysis will be done using the PP population.

The Poolability will be examined at two levels:

1. Location of site based on US versus outside US (OUS)
2. Across individual sites regardless of location

Descriptive statistics of the co-primary safety endpoint will be presented by location (US and OUS) and by site. To test the poolability across US and out of US safety data, a logistic model will be used. In this model the dependent variable is occurrence of AE, and independent variables will include treatment group, location (US, OUS), and group-by-location interaction as fixed factors. The term of interest is the potential interaction between the group and location. If the p-value for the interaction is greater than 0.15, then the data will be considered suitable for pooling at the US-OUS location level. If the p-value is less than 0.15 then additional analyses of the impact of the location will be considered, and the corresponding estimate of the difference will be provided.

In this study some sites are expected to enroll a small number of subjects. Having several small sites might prevent the convergence of logistic regression. Should that occur the smallest sites within geographic location will be pooled together until the model converges.

10.3.4.1.5 Subgroup Analyses for Primary Safety Endpoint

The impact of different covariates on the primary safety outcome will be evaluated. The following covariates will be examined:

- Age, divided into two age groups of less than 65 years and greater than or equal to 65.
- Race

If any baseline factor is found to be significantly different between the treatment groups, it will also be tested as a covariate.

Covariate analyses for the primary safety endpoint will be done using logistic regression. Testing will focus on the covariate by treatment interaction to assess whether safety is dependent on covariate levels. In addition, descriptive statistics by covariate level will be presented.

Each covariate will be evaluated separately.

10.3.4.2 Co-Primary Efficacy Endpoint and Analysis

10.3.4.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is a binary assessment of whether a subject obtains at least a 25% reduction at 21 days post-implantation in the volume of the rectum receiving greater than or equal to 70 Gy (V_{Rectum} 70). The primary efficacy endpoint will be assessed only for subjects who are randomized to the *ProSpace Group* and receive the ProSpace device.

10.3.4.2.2 Primary Efficacy Analysis

The primary efficacy analysis will be done using the PP population.

The primary effectiveness analysis will be completed using a one-sided 0.025 exact binomial test. If we denote v_e to be the percentage of subjects meeting the V_{Rectum} 70 success criteria in the *ProSpace Group*, the primary hypothesis is as follows:

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

The exact binomial 95% CI for the success rate will also be provided. The SAS code for analyzing the primary efficacy endpoint for the *ProSpace Group* subjects is as follows:

```
PROC FREQ ;
       TABLES V70 / BINOMIAL (P=0.75) ;
       EXACT BINOMIAL ;
       RUN ;
```

where V70 is a binary variable indicating whether a subject achieved at least a 25% reduction in V_{Rectum}70 (1 = response, 0 = no response).

10.3.4.2.3 Sensitivity Analysis for Primary Efficacy Endpoint

To evaluate the potential impact of missing data on the primary efficacy endpoint, a tipping point analysis will be performed that considers all possible imputations of the missing data. The analysis will be based on the ITT population.

10.3.4.2.4 Poolability Analysis for Primary Efficacy Endpoint

Poolability analysis will be done using the ProSpace PP population.

The Poolability will be examined at two levels:

1. Location of site based on US versus outside US (OUS)
2. Across sites regardless of location (US or OUS)

Descriptive statistics of the co-primary efficacy endpoint will be presented by location (US, OUS) and by site. To test formally poolability across US and out of US safety data, a logistic model will be used. In this model the dependent variable is the primary efficacy endpoint, and independent variable will be location (US, out of US) as a fixed factor, with baseline V_{Rectum} 70 as a covariate. If the p-value for the location variable is greater than 0.15, then the data will be considered suitable for pooling at the US-OUS location level. If the p-value is less than 0.15 then additional analyses of the impact of the location will be considered, and the corresponding estimate of the difference will be provided.

In this study some sites are expected to enroll a small number of subjects. Having several small sites might prevent the convergence of logistic regression. Should that occur the smallest sites within geographic location will be pooled together until the model converges.

10.3.4.2.5 Subgroup Analyses for Primary Efficacy Endpoint

The impact of different covariates on the primary safety outcome will be evaluated. The following covariates will be examined:

- Age, divided into two age groups of less than 65 years and greater than or equal to 65.
- Race

If the primary efficacy endpoint is found to be significantly dependent on any baseline factor, that factor will also be tested as a covariate.

Covariate analyses for the primary safety endpoint will be done using a logistic regression. Testing will focus on the covariate by treatment interaction to assess whether safety is dependent on covariate levels. In addition, descriptive statistics by covariate level will be presented.

Each covariate will be evaluated separately.

10.3.5 Secondary Endpoints and Analyses

Secondary analyses will be done using the PP population.

10.3.5.1 Secondary Safety Endpoints

Secondary Safety Endpoint #1: Grade 2 Adverse Events

As with the primary safety endpoint, the adverse events qualifying for this secondary safety endpoint will be determined through adjudication by the CEC. This secondary safety endpoint is based on the occurrence of one or more adverse event as follows, as indicated on the CEC CRF:

- Event is indicated to be a Grade 2 or greater Rectal event lasting at least 5 days through the first 183 days (6 months) or
- Event meets one of the relatedness classifications:
    - Event is indicated to possible, probably, or definitely device-related;
    - Event is related to marking or
    - Event is related to the balloon implantation procedure.

As with the primary safety endpoint, subjects will be counted as having an event if one occurs anytime through Day 183 (6 months) from the marking date or as not having an event if they record no events and are followed through at least Day 169 (6 month minus 14 days) from the marking date. This analysis will be based on the CEC classification as identified in Section 10.3.4.1.1. To compare the event rate of the *ProSpace Group* with that of the *Control Group*, the adverse event endpoint will be analyzed using a Fisher's exact test.

Secondary Safety Endpoint #2: EPIC Scores

An additional secondary safety endpoint concerns the degree of all GU acute toxicity as determined by the Expanded Prostate Cancer Index Composite (EPIC). The version used in this study was the EPIC-26 short form. EPIC scores range from 0 to 100 (transformed from Likert scale responses), with higher scores indicative of better functioning.[3] For each of four EPIC domains (Urinary Incontinence, Urinary Irritative, Bowel, and Sexual), the analysis of the EPIC endpoint will evaluate change in EPIC score over time.

[3] Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology. 2000;56(6):899-905.

The domain scores will be summarized descriptively by visit and group along with the change from baseline. Non-parametric Rank-Sum tests will be used to compare change from baseline between groups for each domain at the IMRT midpoint and IMRT final visit.

In addition, for each domain, change from baseline in EPIC score over the course of the study will be evaluated using a mixed model. The independent variables will include visit, treatment group and visit-by-treatment group interaction as factors, continuous baseline EPIC score as a covariate and Subject as a random effect. The model will used with an unstructured covariance matrix. In case it fails to converge, a compound symmetry covariance matrix will be used. Least Squares Means will be used to estimate between-group differences for each visit. Type III tests for the factors will be provided.

In addition, change in EPIC score from Screening to the end of IMRT will be analyzed using a separate analysis. The timing of the final IMRT visit is not fixed across subjects, and therefore, cannot be considered as part of the mixed model described above.

This endpoint will be analyzed using the following regression:

Change in EPIC = Baseline EPIC + Group

The residuals of all linear or mixed model will be evaluated to consider the degree to which the data appear to be normally distribution.

10.3.5.2 Secondary Efficacy Endpoints

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

The distance of the rectal wall from the prostate, as evaluated by the core lab, will also be summarized at baseline and last XRT visit.

All secondary efficacy endpoints are numeric. If change from baseline is approximately normally distributed (or normalized transformation can be identified), the endpoint will be tested using the following regression.

Change from baseline = Baseline.

If an endpoint distribution deviates strongly from a normal distribution, a non-parametric 95% confidence interval for median will be calculated, using percent change from baseline (to account for baseline impact). The Sign-Rank test will be provided for change from baseline comparisons where appropriate to evaluate the null hypothesis that the difference is equal to zero.

10.3.6 Safety

10.3.6.1 Adverse Events

An adverse event (AE) is as any clinically significant unfavorable and unintended medical occurrence, including any abnormal sign (e.g., physical exam), symptom, or disease, whether or not it is considered related to the device being studied in a subject.

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 as by degree of severity.

AEs will be characterized by CEC adjudication, when available, for marking/implantation procedure-relatedness, device-relatedness, IMRT-relatedness, rectum-relatedness, and seriousness. Marking/implantation procedure relatedness adjudication will be further subdivided into relatedness to ProSpace implantation, marker implantation, administration of anesthesia, and use of foley catheter. If there are AEs for which the CEC determination for procedure relatedness or seriousness differs from the determination of the study site, the site-reported AE determinations will be listed separately.

Any AEs reported prior to the marking/implantation procedure will be listed as medical history. AEs that begin during or after the marking/implantation procedure will be counted and listed as AEs. If an AE is specified as starting before the marking/implantation procedure, any event with an increase in severity reported during or after the procedure will be counted and listed as an AE. All AEs will be summarized by treatment group.

Unless otherwise specified, summary counts of AEs will be the number of subjects reporting AEs and not the number of events reported. If the same AE is reported multiple times for the same subject, it will only appear once for that specified treatment and category in the summary tables.

The following AE summaries will be provided:

- Overall Summary of AEs, which will summarize all events, all device-related events, all procedure-related events, all serious events, all device-related serious events, and all procedure-related serious events
- All AEs by Type
- All AEs by Type and Timing (based on AE start date) (1-30 days, 31-210 days, and greater than 210 days post-marking/implantation)
- Device-Related AEs by Type
- Procedure-Related AEs by Type
- Severe AEs of all Type
- Unanticipated Adverse Device Effects, if any
- Adverse Events with Site-CEC Differences

10.3.6.2 Perineal Healing Status

Perineal healing status will be summarized as “healed”, “healing”, or “infected” with descriptive statistics for both groups. Summaries will be provided with frequencies and percentages for each week of IMRT, as well as for the final IMRT visit. Since the timing of the final IMRT visit is subject-dependent, the length of IMRT in weeks will also be summarized by number of subjects (N), mean, median, standard deviation, minimum, and maximum.

10.3.6.3 Physical Examination

Physical examination results will be provided in by-subject listings including clinically significant abnormalities.

11 References

HHS, FDA. Guidance for industry: E9 Statistical Principles for Clinical Trials. 1998.

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Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology. 2000;56(6):899-905.

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