Statistical Analysis Plan

Improving Quality of Life of Prostate Cancer Survivors with Androgen Deficiency

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1.0 Introduction

This statistical analysis plan (SAP) provides details of the statistical methods for data collected as outlined in the protocol for the project "Improving Quality of Life of Prostate Cancer Survivors with Androgen Deficiency" and describes the analysis conventions to guide the statistical programming work.

All analyses will be performed using SAS Version 9.4 or higher (SAS Institute, Inc., Cary, NC 27513) under the UNIX operating system or R version 4.2.0 or higher. The SAP will be signed off by the Principal Investigator and the Chief Biostatistician before the study database is locked.

This SAP will *not* be updated in case of future (administrative or minor) amendments to the protocol unless the changes have impact on the analysis of study data described here.

2.0 Study Background

Prostate cancer (PCa) will affect 1 in 8 American men in their lifetime, with 313,780 new cases projected to occur in the United States in 2025 (1). The majority of men diagnosed with PCa have low-grade, organ-confined prostate cancer and excellent prospects of long term survival (1-5). Excellent survival in men with prostate cancer has focused attention on the high prevalence of sexual dysfunction, physical dysfunction, and low energy, which are important contributors to suboptimal health-related quality of life (HRQOL) among survivors (6-9). The pathophysiology of these symptoms - sexual dysfunction, low energy, and physical dysfunction - after radical prostatectomy is

multifactorial, but androgen deficiency is a frequent (10-12) and important remediable contributor to these symptoms that are associated with to poor HRQOL (6,13-16). Testosterone replacement therapy (TRT) improves these symptoms in men with hypogonadism, who do not have prostate cancer (17-21). However, neither the safety nor the efficacy of TRT has been evaluated in a randomized controlled trial in prostate cancer survivors with hypogonadism.

Testosterone promotes the growth of metastatic prostate cancer (21-23) and androgen deprivation causes regression of symptomatic metastatic prostate cancer (23,24) and improves survival in localized advanced prostate cancer (25-27). Therefore, many oncologists and urologists fear giving TRT to prostate cancer survivors. The relationship between testosterone and PCa is complex. Epidemiologic studies have revealed no consistent relationship between testosterone levels and PCa risk (28-31). However, men with Klinefelter syndrome and men with hypogonadism appear to have lower incidence of prostate cancer than the general population (32,33). The studies have found little or no effect of testosterone treatment on intraprostatic androgen concentrations or on the expression of androgen-dependent genes in the prostate (34,35). Case reports and retrospective reviews of TRT in patients with PCa who have undergone radical prostatectomy have reported very low rates of disease recurrence (36-42). In men with high grade prostatic intraepithelial neoplasia(HGPIN)– a group at high risk of developing prostate cancer– TRT for one year did not increase PSA or rates of prostate cancer (43). Thoughtful editorial commentaries have presented cogent arguments for TRT of men with PCa, who are deemed cured of cancer after radical prostatectomy and who are hypogonadal (16,44). However, many professional society

guidelines, citing the lack of safety or efficacy data from randomized controlled trials, list testosterone treatment as a contraindication in men with history of prostate cancer (20,45-47).

In spite of the absence of randomized controlled trials data, the use of TRT to treat hypogonadism in men with history of treated prostate cancer has continued to grow especially among men with low risk of disease recurrence and bothersome symptoms of hypogonadism. The South West Oncology Group (SWOG) patient advocates indicated that this is a high priority question for prostate cancer survivors. The SWOG Survivorship Committee also recognized the imperative for a large RCT of TRT in correcting the symptoms of androgen deficiency among prostate cancer survivors and recommended that if efficacy and safety can be demonstrated in an initial smaller proof-of-concept RCT, a much larger safety and efficacy trial should follow. This RCT was conducted to implement this recommendation of the Survivorship Committee.

3.0 Objective

Primary Objective

The overall objective of the SPIRIT Trial is to determine the safety and efficacy of testosterone replacement therapy (TRT) in men, who have undergone radical prostatectomy for organ-localized, low-grade prostate cancer, have symptomatic testosterone deficiency and a low risk of disease recurrence.

Primary Safety Objective

- To compare the effect of TRT versus placebo on the incidence of biochemical PSA recurrence in men, who have undergone radical prostatectomy for organ-localized, low-grade prostate cancer, have symptomatic testosterone deficiency and low risk of disease recurrence

Primary Efficacy Objective

- To compare the effect of TRT versus placebo on overall sexual activity, assessed using Psychosexual Diary Questionnaire (PDQ) Question 4 score in men, who have undergone radical prostatectomy for organ-localized, low-grade prostate cancer, have symptomatic testosterone deficiency and low risk of disease recurrence

Secondary Objectives

Secondary safety objectives:

  - To compare the effects of TRT versus placebo on the change from baseline in serum PSA levels

  - To compare the effects of TRT versus placebo on the change from baseline in lower urinary tract symptoms, ascertained using the International Prostate Symptom Score

  - We also will compare the incidence of clinical prostate cancer recurrence in the TRT and placebo groups although the incidence of clinical

recurrence in this study population is expected to very small and unlikely to have sufficient power for meaningful statistical comparison.

- To compare the effect of TRT versus placebo on the frequency of erythrocytosis (verified hematocrit increase > 54%)

- The Safety Assessment will involve tabulation of Adverse Events (AEs) and Serious Adverse Events (SAEs), and assessment of differences in event rates as appropriate. Events will be classified according to MedDRA and SOC coding system and tabulated as absolute number of events and number and proportion of participants experiencing one or more event. We will compare the proportions of individuals with one or more events across arms.

Secondary efficacy objectives

- To compare the effect of TRT versus placebo on sexual desire, assessed using Sexual desire will be assessed by DeRogatis Inventory of Sexual Function - Sexual Desire score
- To compare the effect of TRT versus placebo on erectile function, assessed using the erectile function domain of the International Index of Erectile Function (IIEF)
- To compare the effects of TRT versus placebo on energy level, assessed using the Hypogonadism Energy Diary (HED)
- To compare the effect of TRT versus placebo on mood and wellbeing using the Positive and Negative Affective Scale

- To compare the effect of TRT versus placebo on prostate cancer-related quality of life measured using the hormonal and sexual domains of the Expanded Prostate Cancer Index Composite (EPIC). Expanded Prostate Cancer Index Composite Instrument (EPIC-26)
- To compare the effect of TRT versus placebo on self-reported physical function, assessed using physical function component of MOS SF-36 (PF10)
- To compare the effect of TRT versus placebo on performance-based physical function, assessed by measuring stair climbing power with and without a standardized load
- To compare the effects of TRT versus placebo on maximal voluntary muscle strength and muscle power in the chest press and leg press exercise
- To compare the effects of TRT versus placebo on peak aerobic capacity (VO_{2peak}) achieved during cardiopulmonary exercise testing.
- To compare the effects of TRT versus placebo on whole body, appendicular, and trunk lean tissue mass measured using dual energy X-ray absorptiometry (DXA)
- To compare the effects of TRT versus placebo on whole body, appendicular, and abdominal fat tissue mass, measured using DXA

Other Supportive Analyses

- Evaluation of the relationship between changes in total and free testosterone, DHT, and estradiol levels and changes in outcomes in patients randomized to testosterone arm.

4.0 Study Design

4.1 Study Design

This phase 2 efficacy trial will test the hypothesis that TRT in men who have undergone radical prostatectomy for organ-confined, low-grade prostate cancer, and who have symptomatic testosterone deficiency will be safe and efficacious in improving sexual activity, sexual desire, erectile function, health-related life quality, mood, energy, lean body mass, maximal voluntary muscle strength, and loaded stair-climbing power more than placebo.

This phase 2 trial will be conducted at two trial sites: The Research Program in Men's Health, Aging and Metabolism at the Brigham and Women's Hospital in Boston, MA, and the Brady Urological Institute at the Johns Hopkins Medical Institute, Baltimore, MD.

The trial will be a 12-week, randomized, placebo-controlled, double-blind, parallel group trial in community dwelling men, 40 years or older, with PCa who have undergone radical prostatectomy for organ-localized disease (pT2, N0, M0), Gleason score $\leq$ 7 (3+4), who have undetectable PSA ($\leq$0.1 ng/mL using a sensitive PSA assay) for > 2 years after radical prostatectomy, and who have symptomatic testosterone deficiency. The eligible participants will be randomized to one of two intervention groups, using a computer-generated concealed block-randomization scheme with randomly varying blocks and stratification for and age (40 to 60, >60 years), and use of phosphodiesterase 5 inhibitors (PDEIs) (yes, no).

Group A: Testosterone cypionate 100 mg IM weekly

Group B: Placebo injection IM weekly

The participants and the study staff were blinded to the study intervention. Treatment assignment were known only to the Data Coordinating Center and the Investigational Drug Pharmacy.

4.2 Concealed, Stratified, Block Randomization

The participants were randomly assigned to one of two intervention groups in a 1:1 ratio, using a computer-generated concealed block-randomization scheme with randomly varying blocks of 4 and 6, and stratification for and age (40 to 60, >60 years), and use of phosphodiesterase 5 inhibitors (PDEIs) (yes, no).

5.0 Safety and Efficacy Endpoints

5.1 Primary

Primary safety endpoint

- Our primary safety endpoint is the incidence of biochemical recurrence of prostate cancer. Biochemical recurrence is defined as two or more consecutive serum PSA levels of 0.2 ng/mL or higher.

Primary efficacy endpoint

- Our primary efficacy endpoint is the change from baseline in overall sexual activity, assessed using Psychosexual Diary Questionnaire (PDQ) Question 4. Subjects complete the questionnaire daily for 7 consecutive days before each visit. The PDQ covers 3 domains:1) sexual desire, enjoyment, and performance;

2) sexual activity score; and 3) mood. Sexual desire, sexual enjoyment, and mood are rated on a 7-point Likert-type scale from 0 to 7, with 0 indicating none and 7 indicating high. Sexual activity is assessed using a checklist of 12 sexual activities including sexual interactions, masturbation, intercourse, erection, orgasm, and ejaculation on each of the 7 days. The value is recorded as 0 (none) or 1 (any) for each of the sexual activities. Weekly value is the sum of "any" responses for the week. The sexual activity score is the average of the weekly values. The score is 0 if no activity has taken place. Higher values indicate more activity and lower values indicate lower activity.

Secondary Endpoints

Secondary Safety endpoints

- The change from baseline in serum PSA levels
- The change from baseline in lower urinary tract symptoms, ascertained using the International Prostate Symptom Score
- The change from baseline in hemoglobin and hematocrit level
- The incidence of erythrocytosis in the two study arms
- The incidence of clinical prostate cancer recurrence in the two study arms
- The proportion of participants with adverse events and serious adverse events in each study arm

Secondary efficacy endpoints

- Change from baseline in sexual desire, assessed using Sexual desire will be assessed by DeRogatis Inventory of Sexual Function - Sexual Desire score
- Change from baseline in erectile function, assessed using the erectile function domain of the International Index of Erectile Function (IIEF). The International Index of Erectile Function (IIEF) is a 15-item questionnaire that covers 4 domains of sexual function: erectile function, sexual desire, orgasmic function, and intercourse satisfaction. Each question has a potential score of 0 to 5 for a maximal score of 75 for the entire scale. Our focus in this study is on erectile function domain score, which can range from 0 to 30, lower scores indicating poor erectile function, and higher score indicating better erectile function.
- Change from baseline in energy level, assessed using the Hypogonadism Energy Diary (HED). The total HED scale score is the sum of each of the six item weekly scores, with higher scores corresponding to greater energy level. The HED total score is linearly transformed to a scale of 0-100. Lower score indicate lower energy (or more tiredness0 and higher scores indicate more energy (less tiredness).
- Change from baseline in mood and wellbeing using the Positive and Negative Affective Scale
- Change from baseline in prostate cancer-related quality of life measured using the hormonal and sexual domains of the Expanded Prostate Cancer Index Composite (EPIC). Expanded Prostate Cancer Index Composite Instrument (EPIC-26). HRQOL using the hormonal and sexual domains of the Expanded Prostate Cancer Index Composite (EPIC). Expanded Prostate Cancer Index Composite Instrument

(EPIC-26) for Measuring Health-Related Quality of Life Among Prostate Cancer Survivors EPIC QOL is a 26-item questionnaire that assesses quality of life in 5 domains: urinary incontinence, urinary irritation/obstruction, bowel, sexual and vitality/hormonal domain scores. All domains for EPIC-26 are reported on a 0 to 100 score, with higher scores representing favorable HRQOL

- Change from baseline in self-reported physical function, assessed using physical function component of MOS SF-36 (PF10)
- Change from baseline in performance-based physical function, assessed by measuring stair climbing power with and without a standardized load
- Change from baseline in maximal voluntary muscle strength and muscle power in the chest press and leg press exercise
- Change from baseline in peak aerobic capacity (VO_{2peak}) achieved during cardiopulmonary exercise testing.
- Change from baseline in whole body, appendicular, and trunk lean tissue mass measured using dual energy X-ray absorptiometry (DXA)
- Change from baseline in whole body, appendicular, and abdominal fat tissue mass, measured using DXA

Additional supportive analyses

- The association between changes in testosterone levels and changes in outcomes in patients randomized to testosterone arm.

6.0 Sample Size Justification

We initially estimated that 142 men will be needed to test the primary hypothesis based on the following assumptions:

- Two-sided type I error rate of 0.05,
- 90% statistical power
- 12% total loss-to-follow-up with no endpoint information

Our primary outcome is change in sexual activity derived from Psychosexual Daily Questionnaire- question 4(PDQ-Q4) (48). In the TTrials, the effect size of TRT relative to placebo was 0.6 units (49). Some other TRT trials have shown greater increases in sexual activity scores (50,51). To be conservative, here we assumed that the difference of interest in the change in sexual activity between the testosterone and placebo arms over 3 months is 0.6 units (SD 1.3) (17,49). This change is clinically meaningful and patient-important because our analyses of the TTrials data show that the minimal clinically important difference (MCID) for sexual activity using PDQ-4 is 0.6 units (52). Our experience from the TTrials suggests <5% cumulative loss to follow-up over 12 months, and even smaller amounts of missing data over that time (17). To be conservative, we initially assumed up to 12% total loss of information due to attrition and other causes. Under these assumptions, evaluable data on 63 participants per arm will be sufficient to obtain 90% power to detect a between-group mean difference of 0.6 units in PDQ-Q4 at 12 weeks provided the Pearson correlation between baseline and 12 week PDQ-Q4 measures is at least 0.67, which is less than the correlation observed in the T Trials over a one-year period. To account for missingness, we initially planned

to enroll 63/0.88 = 71 participants per arm. Even if the effect size were as small as 0.5 points, this sample size will provide 80% power to detect smaller differences as small as 0.5 points on PDQ-Q4.

Statistical power for secondary endpoints

We hypothesized that the mean between-group difference in change in sexual desire is 2.5 (SD 5). This assumption is reasonable because in the TTrials, the mean difference in sexual desire was 2.9 units. With conservative assumption of 0.5 Pearson correlation coefficient between baseline and 12-weeks measures, the proposed sample size has 90% power to detect this difference. Similarly, we will obtain 90% power to detect between group difference of 2.5 points in change in erectile function (EF) using IIEF (assumed SD 5 points), a threshold deemed clinically significant (53). In the TTrials, the mean between-group difference in EF score was 2.6 ($P<0.001$), which is similar to that observed in meta-analysis of TRT trials in hypogonadal men (54,55). The men enrolled in the TTrials had severe ED at baseline (mean baseline EF score 8); therefore, our assumption of treatment effect is reasonable and conservative.

Assuming mean (SD) LBM changes of 1.8 kg in the testosterone arm and 0.3 kg in the placebo arm, and SD 2.5 kg; effect size (f, 1.5/2.5, 0.60) simulation results indicate that this design achieves >90% power to demonstrate a treatment effect when the type 1 error is set at the 0.05 level with correlation between time points equal to 0.5 and 12% loss to follow-up. In a testosterone trial in HIV-infected men that used a similar dose of testosterone enanthate, a difference of 2.9 kg in fat-free mass was observed between testosterone and placebo groups (55). Testosterone trials in older men that used

smaller doses of testosterone using a transdermal testosterone formulation observed an increase in LBM of ~1.5 to 2.0 kg (50,51,56).

We anticipate that the between-group difference in leg press strength will be 12 kg (SD 18 kg). This assumption is based on testosterone trials in older men (57,58) , HIV-infected men (59), and in COPD (60). A 12 kg increase in leg press strength is clinically significant because a 10 kg increase was associated with improvements in walking speed (61). 63 subjects per group will provide >95% power to detect this effect size. For other secondary endpoints, the statistical power for the assumed treatment effect was> 80%.

To accommodate complete loss to follow-up of up to 12% with no post-randomization primary endpoint data, we initially planned to enroll 71 men per arm for a total of 142 men. As the study progressed, the loss-to-follow rates were substantially lower and even among those who were lost to follow-up, a substantial fraction provided week 6 endpoint data. Accordingly, with the concurrence of the trial's Data and Safety Monitoring Board (DSMB) and the NIA program staff, the target sample size was revised to 134 subjects anticipating that the revised sample size will still provide the same statistical power as originally assumed. The loss of information in the multicenter TTrials in older men was <5% (17).

7.0 Analysis Populations and Important Subgroups

7.1 Analysis Population

The Full Analysis Set (FAS) will include all randomized subjects. Subjects will be categorized according to treatment assigned at randomization. The FAS will be used for

the summary of subjects' disposition, demographics, and baseline characteristics. The FAS will be used for assessment of primary and secondary efficacy endpoints.

The Safety Set will include all randomized subjects who received at least one dose of the study medication. Statistical analyses of treatment effect over time will comprise all randomized subjects, who have baseline and at least one post-randomization measurement.

A modified analysis set for participants censored at any time (and subsequently) that they are deemed treatment noncompliant per protocol, may be also considered and used for sensitivity analyses of efficacy endpoints.

Data from eligible measurements will be included, where eligible is defined as being obtained from questionnaires or scores for which at least 70% of items are non-missing.

7.2 Subgroup analyses

The following subgroup analysis may be carried out:

- By (40 to 60, >60 years)
- PDE5I use (yes, no)

Additional sensitivity analyses of primary and some secondary endpoints adjusting for adherence and fidelity measures (number of exercise session, total work done during the exercise, and effort level during training) may be undertaken, recognizing that the collection of the adherence measures by study participants during home-based exercise may be variable, especially during the COVID-19 pandemic.

7.3 Analysis Conventions

7.3.1 Definition of Baseline

Baseline on each outcome measure will be defined as the last available measurement obtained prior to the first dose of study drug (defined as on or before Day 1)

7.3.2 Definition of Visit Windows

Definitions of the visit windows (baseline and on-treatment) are described in the study protocol.

7.3.3 Demographics, Baseline Characteristics, Medical History and Study Drug Exposure

Baseline Characteristics

Descriptive analyses of baseline characteristics will be conducted in the Full Analysis Set that includes all randomized participants. Safety analyses will be conducted in the Safety Set that included all randomized participants who received at least one dose of study drug. We will assess the distributional characteristics of outcomes and covariates. Data collected in this study will be documented using summary tables. Statistics for continuous variables will include mean, standard deviation, median, quartile range, minimum, maximum, and sample size for each treatment group, and two-sided 95% confidence intervals of the mean difference between the treatment groups. Binary variables will be described with frequencies, percentages, and two-sided 95%

confidence intervals of the difference in percentages between treatments. Where appropriate, transformation of variables to combat skew, or other irregularities will be employed. Comparability of groups will be assessed using graphical methods.

Treatment Exposure and Adherence

Adherence with the study drug will be computed by dividing the total number of doses that were administered, expressed as a percent of the total number of doses that should have been administered per protocol during the intervention period.

Interim Analysis

No interim analysis is planned for this sub-study.

Multiplicity Testing Procedures for Type-I Error Control

Type I error adjustments for multiple comparisons are not planned for efficacy endpoints, subgroup analyses, supportive analyses or sensitivity analyses for this sub-study.

7.4 Analysis of Endpoints

7.4.1 Primary Efficacy Analysis

The effect of the multimodality intervention on the change over time in sexual activity score in the TRT versus placebo groups will be analyzed using the mixed model repeated measures (MMRM) regression. Change will be defined as the difference from the baseline value. Models will consider visit, treatment effect, visit-by-treatment

interaction, stratification factor (age and PDE5I use) and baseline value as fixed effects. Repeated measure effect will be considered at the participant level. Unstructured covariance matrix will be assumed, however if convergence of the model is not achieved, then a compound symmetry structure will be utilized. Effects of intervention over the treatment period will be calculated as an average score from 6 and 12-week visits, and will be extracted, along with two-sided 95% confidence intervals and P values, from the mixed-model framework.

Sensitivity analyses of treatment effect may also be performed where appropriate after including in the model other fixed effects such as stratification factor (age, PDE5I use), and adherence measures.

7.4.2 Analysis of Secondary Efficacy Endpoints

The intervention effects on secondary outcomes (e.g., sexual desire, erectile function, energy, mood, wellbeing measures) will be analyzed using an approach similar to that for the primary outcome, using mixed effects linear regression model controlling for stratification factor and baseline values, accounting for repeated measures at the participant level. Changes in lean and fat mass, 1-RM strength, stair climbing power, and measures of aerobic capacity derived from the cardiopulmonary exercise test will be analyzed by ANCOVA model with treatment and baseline value included with an approach similar to that for Aim 1.

Sensitivity Analyses will determine if pre-specified covariates influence the effect estimates. We will use a dimensionality-reduction strategy, using propensity scoring as a global adjustment factor. The following variables may be considered: age (40-60,

>60), PDE5 use and adherence. Additional covariates may be incorporated based on exploratory analyses. We will perform per-protocol analyses on completers. Also, per-protocol analysis of subjects, who complete the trial, adjusting for adherence will be performed.

Treatment Adherence will be assessed as the proportion of scheduled injections actually administered divided by the number of injections that should have been administered. A sensitivity analysis may employ adjustment for adherence.

Analyses will not be adjusted for multiple comparisons because the hypotheses being tested are pre-specified; furthermore, the outcomes are highly correlated, making such adjustments overly conservative.

Missing data

All subjects who are randomized will be included in the analyses (intention-to-treat) regardless of adherence. If deemed appropriate, we may utilize multiple imputation by chained equations to generate plausible values for both missing outcomes and covariates simultaneously. This method allows for plausible association between covariates of binomial or multinomial distributions for discrete variables, and can accommodate the clustering of measurements. At least 50 replicates of the analysis will be generated. Assurance of convergence will be obtained using graphical methods. As an additional check against bias, we will employ multiple other methods to challenge these assumptions of missingness at random, including multiple sensitivity analyses; list-wise complete analyses; and pattern mixture models of outcomes.

7.4.3 Safety Analyses

Analyses of biochemical recurrence will utilize a proportional hazards regression model for discrete time. The estimated effect of testosterone and its 95% two-sided confidence interval will be extracted from the model. Statistical tests comparing two treatment arms will be supported by log-rank test and Kaplan-Meier estimates of the incidence function (cumulative event rates over time) obtained for each intervention group. Potential confounding factors will be considered in sensitivity analyses for secondary outcomes; however, these analyses will be contingent on sufficient number of events occurring during the study duration.

Absent intervention, the clinical prostate cancer recurrence rate in this group of men should be <0.5% over 10 years (2-4,24,62), so that few, if any clinical recurrences, are expected in the placebo arm over the three-month trial duration. We likewise anticipate few if any recurrences among subjects randomized to testosterone. To ensure that analyses are sensitive to even limited evidence of safety concerns, we will conduct a **one-sided** comparison of the proportion of subjects experiencing events in each arm using a Fisher's exact test with type-I error probability set at 0.20, as recommended by some FDA panels. Assuming clinical recurrence risk on placebo is 1%, this comparison will have 85% power to detect an increased risk of 10% in the testosterone arm. It is acknowledged here that the total number of events observed may not support these analyses (e.g. regression models) described above. In the case that models are not practicable, descriptive alternatives will be employed.

The Safety Assessment will involve tabulation of Adverse Events (AEs) and Serious Adverse Events (SAEs), and assessment of differences in event rates as appropriate. Events will be classified according to MedDRA and SOC coding system and tabulated as absolute number of events and number and proportion of participants experiencing one or more event. Testing of differences between the proportions of individuals with one or more events across arms will use multiple regression analyses with control for design effects.

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