## 1.0 Title Page

# Clinical Study Protocol M16-100

# Testosterone Replacement therapy for Assessment of long-term Vascular Events and efficacy ResponSE in hypogonadal men (TRAVERSE) Study

## Incorporating Amendment 1, 2, and 3

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|---|---|
| Investigational Product: | AndroGel 1.62% |
| Date: | 06 May 2021 |
| Development Phase: | 4 |
| Study Design: | This is a Phase 4, randomized, double-blind, placebo-controlled, multicenter study of topical testosterone replacement therapy (TRT) in symptomatic hypogonadal men with increased risk for cardiovascular (CV) disease. |
| Investigators: | Investigator information is on file at AbbVie |
| Sponsor: | Testosterone Replacement Therapy (TRT) Manufacturer Consortium acting through AbbVie Inc. *Members of the Consortium on File |
| AbbVie Emergency Contact: | [redacted] MD<br>AbbVie<br>General Medicine<br>1 North Waukegan Road<br>North Chicago, IL 60064<br>Phone: [redacted]<br>Mobile:<br>Emergency 24-hour Number: +1 973-784-6402 |

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

## 1.1 Protocol Amendment: Summary of Changes

**Previous Protocol Versions**

| Protocol | Date |
|---|---|
| Original | 15 December 2017 |
| Amendment 1 | 26 February 2018 |
| Amendment 2 | 13 February 2019 |

The purpose of this amendment is to:

- Make COVID-19 related protocol modifications.

  ***Rationale:*** *To assure subjects' safety, maintain compliance with good clinical practice (GCP), and minimize risks to trial integrity.*
- Updated Section 3.2 to include information on re-evaluation of benefits and risks to subjects participating in the study.

  ***Rationale:*** *Necessary protocol modifications due to COVID-19 pandemic.*
- Updated Section 5.1 to increase screening period to 90 days.

  ***Rationale:*** *Optimize screening window time in order not to screen fail subjects due to COVID-19 pandemic related logistic challenges such as delayed laboratory test results, potential quarantine of eligible subjects for 14 days, etc.*
- Updated wording in Section 5.1.

  ***Rationale:*** *To align the protocol language regarding the proportion of randomized subjects in CV risk factors and CV disease strata with the closure of enrollment in CV risk factors stratum*
- Updated wording regarding Re-screening.

  ***Rationale:*** *To clarify subject eligibility for re-screening.*
- Updated Inclusion Criterion 2

  ***Rationale:*** *To align inclusion criterion 2 with exclusion criterion 2 and clarify when Screening Visit 3 with confirmatory testosterone test level is needed to exclude subjects with two testosterone levels of < 100 ng/dL from participation in the study.*

*Hypogonadal men with two testosterone levels < 100 ng/dL (confirmed) need additional evaluation to rule out primary disorders of the hypothalamus, pituitary, and the testis and should not participate in the long-term placebo-controlled trial with a possibility of getting placebo.*

- Added COVID-19 vaccine information to Section 5.2.3.

  ***Rationale:*** *To allow subjects that received COVID-19 vaccine to enroll or continue in the study and capture vaccine under concomitant medications and document adverse event information related to COVID-19 vaccination in EDC.*

- Added COVID-19 information related to virtual visits throughout Section 5.3.1.

  ***Rationale:*** *To allow the subject to complete applicable procedures during virtual visits and clarify how to proceed with study drug dosing if subject is not able to come to the site for in-person visit(s).*

- Updated Section 5.4.1 to clarify discontinuation language.

  ***Rationale:*** *Information provided on how Investigators should discontinue subjects during COVID-19 pandemic.*

- Updated Section 5.5.2.1 to add direct to subject shipment.

  ***Rationale:*** *To allow study drug to be shipped to subjects' home if subjects are unable to come to the site to receive study drug due to COVID-19.*

- Updated Section 6.1.1.1 Adverse Event to update information on how to document adverse events of cancers in EDC.

  ***Rationale:*** *To clarify that Cancers should be reported on AE/SAE form as well as on a separate Cancer Report Form in EDC.*

- Updated Section 6.1.4 to include COVID-19 information related to AEs.

  ***Rationale:*** *Provide guidance on how to capture AEs related to COVID-19 including those leading to study drug discontinuations, and how to document study drug discontinuations related to COVID-19 due to logistical reasons. Information added on how to document MACE related to COVID-19.*

- Updated Section 7.0 contact information and protocol deviations.

  ***Rationale:*** *Added new study team members contact information. Added information on how to document the protocol deviations related to COVID-19.*

- Clarified Section 8.3 randomization information.

  ***Rationale:*** *Align the protocol language regarding proportion of randomized subjects in CV risk factors and CV disease strata with closure of enrollment in the CV risk stratum.*

- Updated Section 9.3 to include COVID-19 modifications.

  ***Rationale:*** *To allow for additional protocol modifications due to COVID-19 pandemic with additional consent (verbal).*

- Updated Section 10.2 vendor information.

  ***Rationale:*** *Updated vendor name change from CRF Health to Signant Health.*

- Added new COVID-19 procedures for questionnaires in Section 10.2.

  ***Rationale:*** *To allow subjects to complete missed questionnaires at unscheduled visits.*

- Updated Appendix B.

  ***Rationale:*** *Updated signatory list with the current team members.*

- Updated Appendix E

  ***Rationale****: To align Appendix E (Endpoint questionnaire form) with Appendix D in the protocol and Appendix C in the CV/Neuro Adjudication Charter; Visit Form (Subject to be queried at each visit). As agreed with the Agency on 15Aug2017, Arrythmia and Syncope are defined as AESI within the protocol, not endpoints. Therefore, they are reported on the AE/SAE form, not on the Endpoint form and are not undergoing adjudication as also agreed with the Agency within the above-mentioned correspondence. Other AESI on the Endpoint Questionnaire form (Hospitalization for Unstable Angina and TIA) are potential endpoints, are reported on the Endpoint form and are undergoing adjudication. Diabetes (new or worsening) is an endpoint.*

- Apply administrative and editorial changes/corrections throughout the protocol.

  ***Rationale:*** *Revised text to provide clarity and improve consistency and readability of the protocol.*

## 1.2 Synopsis

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| **Sponsor:**<br>Testosterone Replacement Therapy (TRT) Manufacturer Consortium acting through AbbVie Inc.<br>*Members of the Consortium on File | **Protocol Number:** M16-100 |
| **Name of Study Drug:** AndroGel 1.62% | **Phase of Development:** 4 |
| **Name of Active Ingredient:** Testosterone | **Date of Protocol Synopsis:** 06 May 2021 |
| **Protocol Title:** Testosterone Replacement Therapy for Assessment of Long-Term Vascular Events and Efficacy ResponSE in Hypogonadal Men (TRAVERSE) Study | |
| **Objective:** To compare the effect of testosterone replacement therapy (TRT) and matching placebo on major adverse cardiovascular events (MACE). Other safety and efficacy endpoints will be evaluated. | |
| **Investigators:** Multi-center | |
| **Study Sites:** Approximately 400 | |
| **Study Population:** Hypogonadal men with increased risk for cardiovascular disease | |
| **Number of Subjects to be Enrolled:** The planned study enrollment is approximately 6,000 subjects based on the projected timing when 256 MACE will occur under the initial assumptions of the annual event rate, subject accrual rate, and study discontinuation rate. The appropriateness of these assumptions and their impact on the overall sample size will be evaluated by blinded review during the course of the study. | |
| **Methodology:**<br>This is a randomized, double-blind, placebo-controlled, multi-center study. All subjects who are randomized will be followed until the study is completed. | |
| **Diagnosis and Main Criteria for Inclusion/Exclusion:**<br>**Main Inclusion:**<br>Men 45 to 80 years of age with low serum testosterone concentrations (< 300 ng/dL) who exhibit hypogonadal symptoms and have evidence of cardiovascular (CV) disease or are at an increased risk for CV disease and who have not been treated with testosterone in the past 6 months.<br>**Main Exclusion:**<br>Men with congenital or acquired hypogonadism for whom long-term therapy with placebo would not be medically appropriate; prostate specific antigen (PSA) > 3.0 ng/mL; men for whom testosterone therapy is contraindicated. | |

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| **Investigational Product:** | AndroGel 1.62% |
| **Dose:** | Five dose levels, titrated in 20.25 mg increments starting from 20.25 mg to 101.25 mg (1.25 g to 6.25 g of gel) |
| **Mode of Administration:** | Topical |
| **Reference Therapy:** | Matching AndroGel 1.62% Placebo |
| **Dose:** | Same as investigational product (above) |
| **Mode of Administration:** | Topical |

**Duration of Treatment:** Enrolled subjects may be on study drug for the entire duration of the study, which may span up to approximately 5 years.

**Criteria for Evaluation:**

**Safety:**

Primary Safety Endpoint: Time to MACE, is defined as time from randomization to first component event occurrence of the composite MACE endpoint. MACE is defined as a composite endpoint consisting of any of the following:

- Nonfatal myocardial infarction (MI)
- Nonfatal stroke
- Death due to CV causes

Secondary CV safety endpoint, is defined as time from randomization to first component event occurrence of the composite endpoint consisting of any of the following:

- Nonfatal MI (note: silent MIs will not be adjudicated or counted toward the non-fatal MI endpoint during this study)
- Nonfatal stroke
- Death due to CV causes
- Coronary revascularization procedures/cardiac percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery

Secondary Prostate Safety Endpoint:

- High grade prostate cancer (Gleason score of 4 + 3 or higher)

Tertiary Safety Endpoints:

- All-cause mortality
- Heart failure events (hospitalization or urgent visit)
- Thromboembolic events including deep vein thrombosis (DVT)/pulmonary embolism (PE)/venous thromboembolism (excluding superficial thrombophlebitis)
- Peripheral arterial revascularization

**Criteria for Evaluation (Continued):**

**Safety (Continued):**

Tertiary Prostate Safety Endpoints:

- Prostate biopsy
- Any prostate cancer
- Acute urinary retention
- Starting pharmacologic treatment for lower urinary tract symptoms
- Invasive prostate surgical procedures (e.g., prostatectomy, transurethral prostate resection, brachytherapy or other prostate surgical procedure) for benign prostatic hyperplasia

**Efficacy Outcome Variables:**

The following efficacy endpoints will be evaluated in sub-studies or analyses of subpopulations:

1. Improvement in sexual function in hypogonadal men with low libido
2. Remission of depression in hypogonadal men with late-onset, low grade persistent depressive disorder (PDD) (dysthymia)
3. Reduction in incidence of clinical fractures
4. Correction of anemia in subset of subjects with Baseline anemia
5. Reduction in progression from pre-diabetes to diabetes

**Statistical Methods:**

**Analysis Sets:**

The following data sets will be used for the analyses of safety and efficacy endpoints for this study:

The Full Analysis Set (FAS) comprising all randomized subjects. Subjects will be categorized according to treatment assigned at randomization. The FAS will be mainly used for the summary of subjects' disposition and summary of subjects' demographics and Baseline characteristics for the study.

The Safety Set comprising all randomized subjects who receive at least one dose of study drug (TRT or placebo). Subjects will be categorized according to treatment received. Unless otherwise specified, the Safety Set will be used for the analysis of all safety endpoints of the study.

The Efficacy Analysis Sets (EAS) are pre-specified subgroups of the FAS comprising of eligible subjects from the main study who satisfy the criteria for sub-studies for sexual function, PDD, bone fracture, anemia and diabetes. The EAS will be used for the analyses of these sub-studies (Section 5.3.3 and Appendix O). For instance, the EAS for the analysis of sexual function sub-study will include subjects with Baseline DISF-SRII Section I: Sexual Desire domain score $\leq 20$.

**Safety:**

The primary endpoint of the study, time to MACE, is defined as time from randomization to first component event occurrence of the composite MACE endpoint. Time to MACE for subjects who do not experience an event in study will be right-censored at the time of their last available observation. Primary treatment comparison will be based on the hazard ratio of MACE for TRT compared to placebo observed in the Safety Set. The primary statistical criterion for establishing non-inferiority of TRT will be to exclude a hazard ratio (HR) of 1.5 at the upper limit of a 95% two-sided confidence interval (CI). Kaplan-Meier (KM) estimates of the survival curves of time to first MACE for TRT and placebo will be derived.

**Statistical Methods (Continued):**

**Safety (Continued):**

Subjects will continue to be followed for the protocol-specified CV events until completion of the study or death, regardless of whether they continue on treatment or not (unless consent to obtain follow-up information has been withdrawn). These analyses for the primary endpoint will be repeated for the FAS as supportive analyses. The principal sensitivity analyses will also be performed using events that occurred during treatment or within 365 days post-treatment.

Adverse Events of Special Interest (AESI), adverse events (AEs) leading to study drug discontinuation and serious adverse events (SAEs) will be summarized by treatment group and overall in descending order of overall frequency by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT), as well as in a lexicographic order by system organ class (SOC) and MedDRA PT. Additionally, AESI, AEs leading to study drug discontinuation and SAEs will also be summarized by the relationship to study drug and their maximum severity.

**Efficacy Assessments:**

While the primary objective is to evaluate CV risk in middle-aged and older hypogonadal men treated with TRT, this study presents an opportunity to examine a number of efficacy endpoints in a much larger population and for longer treatment duration than other studies reported to date. This study will assess the efficacy of TRT versus placebo for these co-morbidities in sub-studies or analyses of subpopulation:

- **Sexual Function:** Will examine whether TRT (relative to placebo) improves overall sexual activity, sexual desire, and erectile function.
- **Persistent Depressive Disorder (PDD):** Will examine whether TRT (relative to placebo) improves depressive symptoms in men with low-grade, late-onset PDD (dysthymia).
- **Bone Fracture:** Will examine the effect of TRT (relative to placebo) on the incidence of adjudicated clinical bone fractures.
- **Anemia:** Will examine the efficacy of TRT (relative to placebo) in correcting anemia in middle-aged and older hypogonadal men.
- **Diabetes:** Will examine if TRT (relative to placebo) is associated with a lower rate of progression to Type 2 diabetes mellitus in middle-aged and older hypogonadal men with pre-diabetes at Baseline.

Statistical comparisons will be made for these efficacy variables between the active- and placebo-treatment groups.

## 1.3 List of Abbreviations and Definition of Terms

**Abbreviations**

| | |
|---|---|
| 5-ARI | 5-Alpha Reductase Inhibitor |
| AE | Adverse event |
| AESI | Adverse events of special interest |
| ALT | Alanine aminotransferase |
| ARO | Academic Research Organization |
| AST | Aspartate aminotransferase |
| BMD | Bone mineral density |
| BMI | Body mass index |
| BPH | Benign Prostatic Hyperplasia |
| BSSR | Blinded Sample Size Re-estimation |
| BUN | Blood urea nitrogen |
| CABG | Coronary artery bypass graft |
| CBC | Complete blood count |
| CEC | Clinical Events Committee |
| CI | Confidence interval |
| CKD | Chronic Kidney Disease |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| COPD | Chronic Obstructive Pulmonary Disease |
| COVID-19 | Coronavirus Disease – 2019 |
| CRF | Case report form(s) |
| CRO | Clinical Research Organization |
| CV | Cardiovascular |
| CVOT | Cardiovascular outcomes trial |
| D | Diagonal |
| DBP | Diastolic blood pressure |
| DEA | Drug Enforcement Administration |
| DHEA | Dehydroepiandrosterone |
| DHT | Dihydrotestosterone |
| DISF-SRII | DeRogatis Interview for Sexual Function – Self Report (Male) |
| DMC | Data Monitoring Committee |
| DRE | Digital rectal exam |

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|---|---|
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders |
| DTP | Direct-to-patient |
| DVD | Digital versatile disc |
| DVT | Deep vein thrombosis |
| EAS | Efficacy Analysis Set |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form(s) |
| EDC | Electronic data capture |
| eGFR | Estimated Glomerular Filtration Rate |
| EOS | End of Study |
| EP | Endpoint |
| ePRO | Electronic patient reported outcome |
| ESC | Executive Steering Committee |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FV | Final Visit |
| GCP | Good Clinical Practice |
| GDS-15 | Geriatric Depression Scale |
| GGT | Gamma-glutamyl transferase |
| GnRH | Gonadotropin-releasing hormone |
| Hct | Hematocrit |
| HDL-C | High-density lipoprotein cholesterol |
| Hgb | Hemoglobin |
| HbA1c | Hemoglobin A1c |
| HIS-Q | Hypogonadism Impact of Symptoms Questionnaire |
| HR | Hazard ratio |
| hsCRP | High-sensitivity c-reactive protein |
| ICH | International Conference on Harmonization |
| IND | Investigational New Drug |
| IEC | Independent Ethics Committee |
| IIEF-5 | International Index of Erectile Function (5 question version) |
| IRB | Institutional Review Board |
| I-PSS | International Prostate Symptom Score |

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| IRT | Interactive Response Technology |
| KM | Kaplan-Meier |
| LAD | Left Anterior Descending |
| LCX | Left Circumflex Artery |
| LDL-C | Low-density lipoprotein corrected |
| LM | Left Main |
| LTFU | Lost to follow-up |
| MACE | Major Adverse Cardiac Event |
| MCH | Mean Corpuscular Hemoglobin |
| MCHC | Mean Corpuscular Hemoglobin Concentration |
| MCV | Mean Corpuscular Volume |
| MDD | Major depressive disorder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Myocardial infarction |
| mRS | Modified Rankin Scale |
| OM | Obtuse Marginal |
| OTC | Over-the-counter |
| PCI | Percutaneous coronary intervention |
| PCPT | Prostate Cancer Prevention Trial |
| PDA | Posterior Descending Artery |
| PE | Pulmonary embolism |
| PD | Premature discontinuation |
| PDD | Persistent depressive disorder |
| PDQ | Psychosexual Daily Questionnaire |
| PGI-I | Patient Global Index of Improvement |
| PHQ-9 | Patient Health Questionnaire-9 |
| PRO | Patient Reported Outcomes |
| PSA | Prostate specific antigen |
| PT | Preferred term |
| QTcF | QT interval corrected for heart rate (Fridericia's correction formula) |
| RBC | Red blood cell |
| RCA | Right Coronary Artery |
| RI | Ramus Intermedius |
| RMST | Restricted mean survival time |

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|---|---|
| S | Septal |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SBP | Systolic blood pressure |
| SOC | System organ class |
| SV1 | Screening Visit 1 |
| SV2 | Screening Visit 2 |
| SV3 | Screening Visit 3 |
| T | Testosterone |
| TA MD | Therapeutic Area Medical Director |
| TIA | Transient Ischemic Attack |
| TOM | Testosterone in Older Men Trial |
| TRT | Testosterone Replacement Therapy |
| TTE | Time to Event |
| ULN | Upper limit of normal |
| UTI | Urinary Tract Infection |
| US | United States |
| WBC | White blood cell |

## Definition of Terms

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| AbbVie TA MD | AbbVie Therapeutic Area Medical Director |

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# 3.0 Introduction

Testosterone products have been approved in the United States (US) for over 50 years for the treatment of testosterone deficient men. These products are currently indicated for the treatment of congenital or acquired primary hypogonadism and hypogonadotropic hypogonadism in men.[1]

Hypogonadism is an endocrine disorder characterized by absent or deficient testosterone levels along with signs and symptoms of androgen deficiency, including delayed development or regression of secondary sexual characteristics, impaired sexual function, impaired sense of well-being, depressed mood, decreased muscle strength associated with a loss of muscle mass, and reduced bone mineral density (BMD).[2-7]

Current guidelines for the use of testosterone replacement therapy (TRT) outline the appropriate assessment and monitoring of men who are candidates for testosterone therapy. Key components of the Endocrine Society Guidelines[2] include criteria for selecting candidates with signs and symptoms consistent with hypogonadism and documented evidence of low testosterone levels, for whom TRT may be indicated. The Endocrine Society Guidelines also offer recommendations for confirmatory testing of serum testosterone concentrations, additional evaluation, and TRT.[2]

**Cardiovascular (CV) Safety of Testosterone**

In 2010, the Food and Drug Administration (FDA) began an investigation of the CV safety of approved testosterone products after a small, placebo-controlled testosterone trial in elderly men (TOM Trial) was discontinued prematurely due to increased frequency of CV events in the active TRT treatment arm. After reviewing the TOM Trial results and other available published literature, the FDA determined that there was insufficient evidence to conclude that testosterone therapy in older men was associated with an increased risk of adverse CV outcomes.[8,9] In late 2013 and early 2014, two publications[10,11] based on retrospective observational data reported a possible association with the use of TRT and adverse cardiac outcomes in patients treated with TRT versus matched control groups. These studies had a number of limitations such that

conclusions on causality between TRT and CV outcomes could not be established.[9,12,13] Additionally, other epidemiologic studies published prior to and following the above studies observed no increased CV risk, or risk reduction.[14-20]

**Rationale for a CV Safety Study of Testosterone in Hypogonadal Men**

A 2014 FDA Advisory Committee examined the CV safety of testosterone and recommended that a CV outcome study be conducted. FDA requested that testosterone manufacturers work together to conduct an adequately sized study to rule out increased CV risk in hypogonadal men treated with TRT. The rationale for such a study includes the conflicting data for a signal of CV risk in men treated with testosterone and the lack of robust, registration-level clinical efficacy data for TRT in men with hypogonadism associated with aging or co-morbidities. The current TRAVERSE study is designed to fulfill the FDA requirement for a CV safety study as the primary research objective with other safety and efficacy endpoints included as secondary objectives.[9,21] The primary objective of this study is to assess the CV (including coronary cerebrovascular and peripheral vascular) safety of TRT compared to placebo in men with a history of CV disease or with multiple CV risk factors by measuring the treatment effect on adjudicated major adverse cardiovascular events (MACE) including non-fatal myocardial infarction (MI), non-fatal stroke and CV death.

Given the unique nature of this study, which will study the effects of testosterone treatment compared to placebo in several thousand men for up to 5 years, the study will also examine as secondary outcomes the impact of therapy on development of high grade prostate cancer and several efficacy outcomes whose rationale is described below.

**Impact of Testosterone Replacement on the Incidence of High-Grade Prostate Cancer**

Evidence of a relationship between TRT and the incidence of prostate cancer is mixed. In the Baltimore Longitudinal Study of Aging, aggressive prostate cancers were reported to be associated with higher levels of total and free testosterone.[22] Also, testosterone administration increases prostate specific antigen (PSA) in men and can promote the

growth of metastatic prostate cancer.[23] On the other hand, most population-based studies have not associated high total or free testosterone levels with increased cancer risk,[24-26] and an analysis of the placebo arm from the Prostate Cancer Prevention Trial (PCPT) found no significant associations of total or free testosterone and risk of total, low (Gleason < 7) or high-grade (Gleason 7 – 10) prostate cancer.[27,28]

Occult prostate cancer is common in middle-aged and older men, and the prevalence increases with increases in PSA and age.[27,29] The designers of the current study recognize that testosterone therapy increases PSA in circulation and thus, in the current study more men randomized to testosterone will be referred for prostate evaluation and possible biopsy based on this laboratory finding. Consequently, testosterone-treated men may have an increased risk of detection of subclinical prostate disease that was present prior to treatment.[25,30,31] This inherent surveillance bias could result in a greater number of prostate biopsies that are positive for low-grade indolent prostate cancers in men randomized to the testosterone arm than in those randomized to the placebo arm. With this recognition of the inherent detection bias from testosterone treatment leading to the detection of low grade prostate cancers, this study will assess the effect of testosterone and placebo on the development of high grade prostate cancer, defined as Gleason 4 + 3 or greater.

**Benefits of Testosterone Therapy**

While it has been suggested that the benefits of testosterone treatment are clearer in "classical hypogonadism," data on TRT risks and benefits specifically in men without structural or genetic abnormalities that cause "classical hypogonadism" with very low circulating testosterone have only begun to emerge.[32,33-35] In men with a variety of comorbid conditions that result in testosterone levels below the accepted normal range (e.g., obesity, diabetes or other chronic diseases), TRT has been shown to increase lean body mass and bone mineral density (theoretically reducing the risk of bone fractures), decrease fat mass and improve sexual desire in most studies, while improvements in mood and energy have been inconsistent.[32,33-36] Low testosterone levels are implicated as one of the many factors causing anemia, which is more prevalent with advancing age,[37] and

testosterone is known to increase hemoglobin (Hgb) levels, thereby presenting a potential benefit of TRT in hypogonadal men with anemia.[34,38-41] Also, there is evidence to support a hypothesis that TRT may slow the progression to diabetes in hypogonadal men with pre-diabetes.[43-45] There are limited data in men with age-associated and/or comorbidity-associated hypogonadism utilizing patient reported outcomes (PRO) tools created following the FDA guidance for PRO development.[9,21,32] Given the opportunity that this protocol affords, the TRAVERSE study will analyze the effects of a testosterone gel (AndroGel 1.62%)[1] in middle aged and older men with CV risk factors and/or CV disease on a number of efficacy endpoints that have demonstrated some level of responsiveness in previous TRT studies and that otherwise could not be studied in smaller studies of shorter duration. Specifically, the TRAVERSE study will address the effect of TRT on improving the following efficacy variables versus placebo:

- sexual activity and function in subjects with low libido at Baseline
- remission of persistent depressive disorder (PDD) in subjects with low-grade PDD at Baseline
- adjudicated clinical bone fractures
- correction of anemia in subjects with anemia at Baseline
- progression to diabetes in subjects with pre-diabetes at Baseline

## 3.1 Differences Statement

This is the first placebo-controlled study that is adequately sized to characterize the impact of TRT or identical placebo on the incidence of MACE in hypogonadal men.

## 3.2 Benefits and Risks

The efficacy of AndroGel 1.62% is demonstrated by its ability to increase serum total testosterone (T) levels by the absorption of testosterone through the skin when applied topically. The objective of TRT in hypogonadal men is to replace testosterone within the eugonadal range for healthy men (300 – 1000 ng/dL). Replacement of testosterone levels into the eugonadal range in hypogonadal men should lead to restoration of androgenic

effects such as improvements in libido and mood, increased lean mass, decreased fat mass and increased BMD.[2] The aforementioned endpoints have been examined in placebo-controlled studies with various levels of supportive evidence depending on the cohorts (hypogonadal, eugonadal, mixed), and the endpoints examined.

Potential risks of treatment with AndroGel 1.62% include secondary transfer of testosterone to others, increased PSA levels, mood swings, increased red blood cell (RBC) count, and skin irritation at the application site.[1]

This study will evaluate the rate of MACE in hypogonadal men at risk for CV disease receiving TRT or placebo for up to approximately 5 years. Additionally, the study will also evaluate as secondary outcomes a limited number of targeted safety (e.g., prostate) and efficacy endpoints, which are patient-important, consistent with symptom domains and/or target organ systems that have demonstrated responsiveness in previous TRT studies, and which will allow the testing of specific efficacy hypotheses in the five domains discussed earlier.

Considering the coronavirus (COVID-19) pandemic, the benefits and risks to subjects participating in this study have been re-evaluated. Based on the limited information to date, no additional risks to study participants diagnosed with COVID-19 are anticipated with the use of Androgel 1.62%.

## 4.0 Study Objective

The primary objective of this study is to compare the effect of TRT and placebo on the incidence of MACE in middle-aged and older hypogonadal men at risk for CV disease. The secondary CV safety endpoint is to compare the effect of TRT and placebo on an expanded list of CV outcomes including MACE plus coronary revascularization procedures/cardiac percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery.

An additional secondary safety objective is to determine the effect of TRT on the incidence of high-grade prostate cancer in this population. Finally, this study will

evaluate a number of secondary and tertiary efficacy endpoints defined in the sub-studies (see Appendix O).

# 5.0 Investigational Plan

## 5.1 Overall Study Design and Plan: Description

This is a Phase 4, randomized, double-blind, placebo-controlled, multicenter study of topical TRT in symptomatic hypogonadal men with increased risk for CV disease.

The initial planned study enrollment is approximately 6,000 subjects based on the projected timing when 256 MACE will occur under initial assumptions of the annual event rate, subject accrual rate, and study discontinuation rate.

There will be approximately 400 sites in North America including Puerto Rico.

An Interactive Response Technology (IRT) system will randomize subjects to receive either topical testosterone or placebo in a 1:1 ratio. Randomization will be stratified by pre-existing CV disease (Yes/No). Titration of testosterone dose will occur in subjects receiving active testosterone, while sham dosage titrations will occur in subjects receiving placebo gel via the non-blinded central IRT system (Section 5.5.3).

The Screening Period is up to 60 days prior to first study drug dose. Subjects may enroll an additional 30 days after the 60-day period due to COVID-19 related issues. If the 90-day screening period is required, sites should contact their monitor or refer to the 90-day extension instructions on how to complete the process in IRT.

Once subjects meet all of the eligibility criteria during Screening, they will be randomized (1:1 ratio) to active study drug or placebo and will be followed until the study ends. Importantly, randomized subjects who elect to temporarily or permanently discontinue study drug (Section 5.4.1) will also be followed until the study ends unless the subject withdraws from the study completely (withdrawal of informed consent Section 5.4.1). Subjects who discontinue study drug will still be asked to follow their regularly scheduled protocol visits specified in Appendix C Study Activities. Subjects who discontinue study

drug will be allowed to restart study drug at any time if medically appropriate (Section 5.4.1).

Periodic blinded overall MACE assessments, coupled with the sample size and duration of treatment to date, will be conducted (e.g., after 4,500 subjects have been enrolled or following 2.5 years of study conduct) to estimate whether or not the sample size and/or the study duration will need to be modified in order to observe at least 256 MACE. AbbVie or designee will make every effort to give sites advanced notice when the recruitment for the study is nearing completion to minimize the risk of a high number of subjects in Screening who may not be allowed to enroll in the study.

During telephone contacts and in-person visits throughout the study, subjects will be asked specific questions pertaining to the possible occurrence of MACE and adverse events of special interest (AESI), as well as the collection of additional information related to ongoing adverse events (AEs) (see Appendix C).

Randomized subjects will return for the Final Visit (FV) (Appendix C) once the Sponsor ends the study. For randomized subjects who discontinue the study prematurely, Premature Discontinuation (PD) Visit case report forms (CRFs) should be completed at the time the subject withdraws consent (e.g., in-person preferably or via a phone visit) from the study or has a fatal outcome (if this information is available). For lost to follow-up subjects, every attempt should be made to contact the subjects to obtain study related information. For these subjects, the FV CRFs should not be completed until the end of the study (Section 5.4.1) so that further study information can be obtained.

Subjects meeting the stopping criteria for study drug (Section 5.4 Removal of Subjects from Therapy or Assessment) will have study drug discontinued and will be followed for all safety events outlined in Appendix D for the duration of the study (Section 6.1.4).

The study is planned to end after at least 256 MACE have been positively adjudicated by Clinical Events Committee (CEC) for the principal sensitivity analysis of the primary

safety endpoint (see Section 8.1.4). Enrolled subjects may be on study drug for the entire duration of the study, up to approximately 5 years.

It is expected that the number of MACE events will be higher in the subjects with pre-existing CV disease. To reach the intended event rate, the study is targeting at least 30% of randomized subjects will satisfy inclusion criteria for pre-existing CV disease criteria (secondary prevention), and up to 70% of randomized subjects will satisfy CV risk factors criteria (primary prevention) combined; the proportions will be monitored and controlled via IRT throughout the study. The Executive Steering Committee (ESC) and AbbVie may decide to cap the cohort of subjects with CV risk factors (i.e., no pre-existing CV disease) if that cohort is found to consistently exceed 70% of the total population enrolled or if the pooled primary event rate falls below projections.

AbbVie or its designee will make every effort to give sites advanced notice when recruitment for the study is nearing completion to minimize the risk of a high number of subjects in Screening who may not be allowed to enroll in the study.

Study data will be monitored by an independent Data Monitoring Committee (DMC) in accordance with standard conduct for clinical outcome studies. Study oversight will occur through an ESC, which will advise AbbVie and the independent DMC. The CEC will be utilized to adjudicate pre-specified CV, prostate and fracture event data during the study. See Appendix D and Appendix E for detailed event reporting and endpoint questionnaire, respectively.

Re-Screening

Subjects who fail to meet the selection criteria or who cannot return for Screening Visit 2 (SV2) or Screening Visit 3 (SV3) within the visit window may be re-screened one time at the discretion of the Investigator once their clinical status changes provided they did not screen fail due to testosterone levels outside the entry criteria.

- If the subject is re-screened within 3 months (90 days) of his initial Screening Visit, then only the necessary procedures to confirm eligibility need to be

performed with the exception of the SV2 PROs (Appendix C). The SV2 PROs will be repeated for all re-screening subjects.

- If the subject has not been re-screened within 90 days of his initial Screening Visit, he is still permitted to re-screen but all of the Screening procedures must be repeated and he must be re-consented.

Men with a Screening Visit 1 (SV1) testosterone level between 300 and 333 ng/dL or men who did not have a confirmed testosterone level < 300 ng/dL at SV2 or SV3 can be re-screened after 3 months following their last visit. Men with two testosterone values < 100 ng/dL cannot be re-screened. All of the Screening procedures must be repeated and the subjects must be re-consented. Re-screened subjects will not receive a new subject number (Section 5.5.3).

## 5.2 Selection of Study Population

Adult male subjects who meet the inclusion criteria and do not meet any of the exclusion criteria will be eligible for enrollment (randomization) into the study.

### 5.2.1 Inclusion Criteria

1. Men whose age is between 45 and 80 years, inclusive, at the time of Screening.
2. Meet the study definition of clinical hypogonadism as evidenced by:

   a) Two serum testosterone levels < 300 ng/dL collected between 5 AM and 11 AM local time. If SV1 level < 300 ng/dL, then proceed to SV2 or if needed, SV3:

   - SV1 level < 300 ng/dL; and SV2 level < 300 ng/dL

     OR
   - SV1 level < 300 ng/dL; and SV2 level between 300 ng/dL and 333 ng/dL; and with a SV3 level < 300 ng/dL
   - If SV1 or SV2 level < 100 ng/dL, then additional SV3 confirmatory testosterone test is needed

   Note: Testosterone levels should be collected at least 48 hours apart.

***AND***

b) Presence of at least one sign or symptom that may be related to low testosterone values and is/are consistent with hypogonadism such as the following:

- Decreased sexual desire or libido
- Decreased spontaneous erections (e.g., morning erections)
- Decreased energy or fatigue/feeling tired
- Low mood or depressed mood
- Loss of body (axillary and pubic) hair or reduced shaving
- Hot flashes

3. Have pre-existing (historical) CV disease as evidenced by at least one disease in Table 1 OR at least three CV Risk Factors from Table 2.

**Table 1. Pre-Existing CV Disease**

| | |
|---|---|
| Coronary Artery Disease | • Acute MI > 4 months before SV1<br>• Coronary artery disease (at least a 50% lesion in two of the major coronary artery distributions including their branches) as documented by angiogram (see Appendix Q for further details)<br>• Coronary revascularization (coronary artery bypass grafting [CABG] or percutaneous coronary intervention [PCI]) > 4 months before SV1 |
| Cerebrovascular Disease | • Stroke excluding hemorrhagic > 4 months before SV1<br>• TIA that required treatment > 4 months before SV1<br>• Catheter-based or surgical revascularization of the carotid or middle cerebral arteries > 4 months before SV1<br>• Extracranial carotid artery stenosis > 50%, excluding intracranial vessels |
| Peripheral Arterial Disease | • Symptomatic peripheral arterial disease (i.e., lower extremity arterial disease documented by ankle/brachial index < 0.9 with claudication or resting limb ischemia obtained in the prior 12 months)<br>• Peripheral arterial revascularization or amputation due to arterial obstructive disease > 4 months before SV1<br>• Peripheral arterial stenosis > 50%<br>• Abdominal aortic aneurysm not due to connective tissue disorders |

**Table 2. Cardiovascular Risk Factors**

| Risk Factor | Definition |
|---|---|
| Hypertension | - Hypertensive and taking prescription anti-hypertensive medication<br>OR<br>- Systolic blood pressure (SBP) > 140 or diastolic blood pressure (DBP) > 90 mmHg during Screening Period |
| Dyslipidemia | - Dyslipidemic and taking prescription anti-dyslipidemic medication<br>OR<br>- Low-density lipoprotein corrected (LDL-C) > 160 mg/dL or high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL during Screening Period |
| Current Smoker | - Current daily cigarette/cigar smoker (e-cigarette smoking alone does not satisfy this criterion) |
| Stage 3 Chronic Kidney Disease (CKD) as defined by eGFR ranges | - Estimated Glomerular Filtration Rate (eGFR) > 30 and < 60 mL/min by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation during Screening Period |
| Diabetes | -Diabetic and currently taking prescription anti-diabetic medication<br>OR<br>- Hemoglobin A1c (HbA1c) ≥ 6.5% or fasting glucose of ≥ 126 mg/dL during Screening Period |
| Elevated hsCRP | - History of high-sensitivity C-reactive protein (hsCRP) ≥ 2.0 mg/L (≥ 0.2 mg/dL) and confirmed at SV2 |
| Documented Historical Agatston Coronary Calcium Score ≥ 75$^{th}$ percentile for age and race (supported by medical records) | - The Agatston coronary calcium score should not be obtained for the purposes of Screening (a link will be provided for calculation of the 75$^{th}$ percentile calcium score) |
| ≥ 65 Years of Age | |

4. Naïve to testosterone replacement, clomiphene, compounded or over-the-counter (OTC) androgenic steroid derivatives and dehydroepiandrosterone (DHEA), including investigational products that may affect the reproductive hormonal system within the past 6 months.
5. Willingness and the ability to apply topical testosterone gel as instructed by the study staff and comply with the requirements of this study protocol.

6. Intact skin surfaces on the upper arms and shoulders where the topical testosterone will be applied.

**Rationale for the Inclusion Criteria**

| | |
|---|---|
| 1 – 4 | To select appropriate subject population with a disease status representative of the target population for evaluation |
| 5 | To select subjects who will comply with study procedures for adequate evaluation |
| 6 | To select subjects who would be expected to have reliable testosterone absorption from the application site |

### 5.2.2 Exclusion Criteria

1. Congenital or acquired hypogonadism for whom long-term therapy with placebo would not be medically appropriate.
2. Two testosterone levels < 100 ng/dL during Screening.
3. Current or recurrent ulcer, erosion, lichenification, inflammation psoriasis, eczema or use of topical cortiosteroids on the upper arms and shoulders. Tattoo application or removal in the region of study drug application within 6 months of Screening.
4. Known skin intolerance to alcohol or allergy to any of the ingredients of the study drug (see AndroGel 1.62% prescribing information).
5. History of treatment with growth hormone, anti-estrogen or estrogen treatment within 90 days prior to Screening.
6. Subjects taking acute course (> 5 days) of opioids or systemic glucocorticoids > 7.5 mg prednisone equivalent per day (e.g., hydrocortisone 30 mg, methylprednisolone 6 mg, or dexamethasone 1.2 mg) for a recent acute condition (e.g., surgery, trauma, or illness) 1 week before SV1 through Day 1 (Note: Chronic daily therapy is allowable).
7. History of prostate (current or in the past) or breast cancer.

8. Severe lower urinary tract symptoms as indicated by an International Prostate Symptom Score (I-PSS) > 19.
9. Prostate nodule or induration as determined by the Investigator on screening Digital Rectal Examination (DRE). Men who have a documented normal DRE within 6 months of SV1 will not require a screening DRE. Prostate enlargement consistent with benign prostatic hyperplasia (BPH) is not an exclusion criterion. Prostate abnormalities where prostate cancer has been ruled out through previous negative biopsies are also not exclusionary.
10. PSA > 3.0 ng/mL; men treated with 5-alpha reductase inhibitors (e.g., dutasteride, finasteride) are eligible for participation as long as PSA levels are not > 1.5 ng/mL.
11. Seeking fertility currently or for the duration of the study.
12. History of untreated, severe obstructive sleep apnea.
13. Body Mass Index (BMI) > 50 $kg/m^2$.
14. Documented MI, coronary revascularization (CABG, PCI), unstable angina, stroke, transient ischemic attack (TIA) requiring treatment, catheter-based or surgical revascularization of the carotid or middle cerebral arteries or procedures to treat/current evidence of critical limb ischemia < 4 months of SV1 or during the Screening period.
15. New York Heart Association Class III or IV heart failure.
16. Sitting SBP > 180 mmHg or < 80 mmHg or sitting DBP > 110 mmHg or < 50 mmHg at any point during the Screening period.
17. HbA1c > 11% at Screening for diabetic subjects.
18. History of unprovoked deep vein thrombosis (DVT), unprovoked pulmonary embolism (PE), or known thrombophilia.
19. Known history of polycythemia vera or secondary polycythemia, such as polycythemia due to untreated sleep apnea or severe chronic obstructive pulmonary disease (COPD).

20. History of major non-cardiovascular surgical procedure (e.g., major abdominal or thoracic procedure) within the 3 months prior to Screening and/or at the time of Screening, a major surgery is scheduled.

21. Any inpatient hospitalizations (duration of hospitalization > 24 hours) or major febrile illness (temperature > 101°F) within 4 weeks prior to Screening.

22. Active malignancy or diagnosed with or treated for cancer within the past 2 years. Subjects with basal and squamous cell carcinoma of the skin that has been successfully treated will be allowed to participate.

23. A current condition, therapy, lab abnormality, history of clinically significant medical or psychiatric conditions or other circumstance or reasons which, in the opinion of the Investigator or the study staff, might pose a risk to the subject, make participation not in the subject's best interest, confound the results of the study (e.g., if subject cannot comply with requirements of the study), make the subject an unsuitable candidate to receive study drug, or interfere with the subject's participation for the full duration of the study.

24. History, suspicion, or evidence of significant drug or alcohol abuse or illicit steroid use within the previous 12 months prior to Screening (SV1), as determined by the Investigator.

25. Clinical laboratory analysis shows any of the following abnormal results:

    a. Hematocrit (Hct) > 50%.

    b. Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN).

26. Severe or end-stage CKD documented by eGFR < 30 mL/min.

27. Has been treated with any unapproved investigational drug within 30 days or five half-lives of the drug (whichever is longer) prior to the first dose of study drug. If the investigational product is known or thought to significantly affect the subject's CV risk profile, the washout period is 6 months prior to Screening (SV1).

28. Subject has a history of any of the following:
    - Major psychiatric disorder that is not controlled with a stable treatment regimen in the opinion of the Investigator.
    - Any suicide attempts within the past year or a response greater than 0 on Question 9 from Patient Health Questionnaire-9 (PHQ-9) at Screening.
29. Subjects who have undergone female to male gender reassignment.

**Rationale for the Exclusion Criteria**

| | |
|---|---|
| 5, 6, 11, 12, 13 | To avoid conditions which constitute a contraindication for testosterone therapy, to reduce the risk to subjects to exclude underlying conditions that would indicate an unstable medical condition, or increase the subject's chances of being discontinued shortly after starting study drug and/or compromise the subject's safety |
| 1, 2, 7, 8, 9, 10, 14 - 23, 25, 26, 28, 29 | To avoid medical conditions that may compromise the ability to identify subjects with the correct diagnosis or to interpret medical importance of clinical results |
| 11, 24 | To exclude subjects who may be at increased risk for protocol non-adherence or PD |
| 3, 4, 27 | To avoid bias in the evaluation of efficacy and safety by concomitant use of other medications or treatments |

### 5.2.3 Prior and Concomitant Therapy

Prescription medications and over the counter aspirin, iron, folate, B12, vitamin D and calcium that the subject is receiving at the time of enrollment, or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency. Other non-prescription medications may be collected in the case of AESI, AEs leading to study drug discontinuation and SAEs.

During each phone contact or in-person visits with subjects who discontinue study drug prematurely, subjects will be asked whether or not they have started on TRT since they discontinued study drug, and if so, the route of administration, frequency and dose will be obtained.

The Therapeutic Area Medical Director (TA MD) or designated personnel should be contacted if there are any questions regarding concomitant or prior therapy(ies).

Prior to study drug initiation, Investigators and/or other study site personnel should inform all participating subjects with known or presumed coronary artery disease that administration of drug products for the treatment of erectile dysfunction (i.e., tadalafil; sildenafil citrate; vardenafil hydrochloride) is contraindicated in subjects using any form of organic nitrate/organic nitrite and may potentiate the hypotensive effect of nitrates. This discussion should be documented in the source document.

**COVID-19 Pandemic-Related Vaccination Guidance**

The impact of M16-100 study drug on COVID-19 vaccination is unknown. However, given the ongoing COVID-19 pandemic, FDA authorized/approved vaccines may be administered during screening and/or treatment period to prevent SARS-CoV-2 infection.

The decision to receive a locally available FDA authorized/approved COVID-19 vaccine should be based on a local guidance and an individual discussion between the treating physician and the subject.

Note: The above guidance applies to all FDA authorized/approved SARS-CoV-2 vaccine doses given as part of the complete treatment course.

These recommendations may be subject to change based on the evolving knowledge around the use of FDA authorized/approved SARS-CoV-2 vaccines in patients, as more data are collected in real-world scenarios and clinical trials.

Any FDA authorized/approved SARS-CoV-2 vaccine information must be documented on the Concomitant Medications eCRF page.

Reactions associated with the FDA authorized/approved SARS-CoV-2 vaccine should be reported as AEs if they meet the protocol reportable AE criteria (See Section 6.1.1.1). If the event meets the criteria for an SAE, then follow the SAE reporting directions (See Section 6.1.5). All protocol defined AEs, medications, permanent study drug or study discontinuation, etc. due to COVID-19 should be noted as such in EDC.

#### 5.2.3.1 Prohibited Therapy

The eligibility criteria list medications that are prohibited prior to study entry (see Section 5.2.1 and Section 5.2.2).

Subjects must not take oral nitrates concomitantly with drug products used to treat erectile dysfunction (i.e., tadalafil, sildenafil citrate, vardenafil hydrochloride).

The following pertains to prohibited medications during the study.

- Compounded or OTC androgenic steroid preparations, supplements or testosterone derivatives
- Topical corticosteroids on the upper arms and shoulders (e.g., hydrocortisone)
- Clomiphene
- TRT from a source outside the study

Subjects must not take any other form of testosterone other than the study drug during the study as stated above. Subjects who receive TRT from a source outside the study after discontinuing study drug are eligible to re-start study drug based on the last study prescribed dose so long as the subjects are at the end of the labeled (package insert) dosing interval for non-study testosterone (Section 5.4.1).

#### 5.2.3.2 Rescue Therapy

Medications containing testosterone treatments or medications known to increase testosterone and used as rescue therapy for hypogonadal symptoms are not permitted during the study.

## 5.3 Efficacy and Safety Assessments/Variables

### 5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures are listed in the following section of this protocol and are summarized in tabular format in Appendix C.

**COVID-19 Pandemic-Related Acceptable Protocol Modifications**

Due to the COVID-19 pandemic, subject visits, excluding Screening, Day 1, Week 2, Week 4, Months 60/Final and Premature Discontinuation Visits, may be conducted virtually via phone or video conference only if in-person visits are not possible.

#### 5.3.1.1 Study Procedures

**Informed Consent**

The subject will sign and date a study-specific Institutional Review Board (IRB)/Ethics Committee (EC) approved informed consent form before any study procedures are performed at or prior to SV1.

Details regarding how informed consent will be obtained and documented are provided in Section 9.3.

**Inclusion/Exclusion Criteria**

Subjects will be evaluated to ensure they meet all inclusion criteria and have none of the exclusion criteria at both Screening and Baseline Visits.

**Cardiovascular (CV) Risk Assessment**

Subjects will be assessed for pre-existing CV disease (Section 5.2.1) or at least 3 CV risk factors (Table 2). CV risk should be assessed prior to SV2 testosterone testing.

**Medical and Surgical History/Alcohol and Nicotine Use**

For all subjects, a complete medical and surgical history will be obtained during the Screening Period. In addition, history of alcohol and nicotine use will be obtained from each subject during the Screening Period. The medical history will be updated on Day 1 prior to dosing. The updated medical history on Day 1 will serve as the Baseline for the clinical assessment.

**Cancer History**

Subject's cancer history will be obtained during the Screening Period, if applicable. The cancer history will be updated on Day 1 prior to dosing. If the subject is given a diagnosis of cancer post-Baseline, then additional information will be collected.

**CV Family History**

The subjects will be asked if their father, mother, brother or sister have a history of heart attacks.

**Height, Body Mass Index (BMI), Weight**

Height will be measured only during the Screening Period (Appendix C) in order to calculate BMI (calculated during Screening Period only); the subject will not wear shoes. Body weight (visits specified in Appendix C) will be measured on a calibrated scale shortly after the subject empties his bladder with the subject in light indoor clothing with pockets empty and without shoes, belts, jewelry or other accessories. Weight may be recorded in kilograms to the nearest 0.1 kilogram or in pounds to the nearest 0.25 pound. If possible, the same scale should be used for all weight measurements.

BMI is defined as the subject weight in kilograms divided by the subject height in meters squared ($kg/m^2$) and should be calculated to the nearest one-tenth unit. All calculations made for the purpose of establishing a subject's eligibility and to be randomized into the study should be recorded in the Screening Visit source documents and CRFs. The following formulas will be used to convert to metric units for calculation of BMI:

Pound (lb) ÷ 2.2 = Kilogram (kg)

Inch (in) × 0.0254 = Meter (m)

BMI calculations will be made by the Investigator or designee during the Screening Period and at Baseline using the following formula:

$$BMI\ (kg/m^2) = weight\ (kg) \div [height\ (m)\ at\ Screening\ Visit]^2$$

**COVID-19 Pandemic-Related Acceptable Protocol Modifications**

During virtual visits, weight measurement may be performed by subject or caregiver as needed and if possible.

**Physical Examination**

A complete physical examination will be performed at SV2. The physical examination at SV2 will serve as the Baseline physical examination for clinical assessment. All other physical examinations as indicated in Appendix C will be symptom-directed examinations.

Any significant physical examination findings not present at Baseline and detected on subsequent examinations will be documented and any significant findings meeting the criteria in Section 6.1.1.1 will be reported.

At any time, a symptom-directed physical examination can be performed as deemed necessary by the Investigator.

**Prostate-Specific Antigen (PSA)**

A blood draw to measure PSA should occur prior to the DRE as prostate manipulation can falsely elevate PSA.

Only men who have a testosterone < 300 ng/dL at SV1 will have a PSA evaluated from that same sample. At Screening, the PSA must be ≤ 3.0 ng/mL (≤ 1.5 ng/mL in men receiving 5-alpha reductase inhibitors).

PSA tests will be collected as specified in Appendix C. PSA values will remain blinded after randomization unless two consecutive PSA values are elevated as defined in Section 6.1.8.

**Digital Rectal Examination (DRE)**

A DRE will be performed as indicated in Appendix C and should be done after the PSA blood draw.

The Screening DRE will not be required if the subject had a previous normal DRE within 6 months of SV1 and the written documentation of the DRE result is provided. Written documentation of the DRE result for on treatment visits will be required for DREs not performed at the study site with the timing windows defined in the Appendix C. An abnormal DRE during the Screening Period will exclude the subject from the study until any prostatic abnormalities have been evaluated and deemed not exclusionary. Any abnormalities found on the DRE during either Screening or Treatment (except benign prostatic enlargement, or BPH) will be recorded and referred to a urologist for further evaluation.

**Vital Signs**

Vital sign determinations of systolic and diastolic blood pressure in sitting position for approximately 5 minutes, pulse rate, respiratory rate, and body temperature will be obtained at visits specified in Appendix C.

**12-Lead Electrocardiogram (ECG)**

A resting (supine for approximately 5 minutes) 12-lead ECG will be performed at the designated study visits as specified in Appendix C. A qualified physician will interpret the clinical significance of any abnormal finding, sign, and date each ECG.

ECG with QT interval corrected for heart rate using Fridericia's correction formula (QTcF) should be reported (or calculated) and documented in the source documents and later transcribed on to the appropriate electronic CRF (eCRF), if QTcF prolongation is observed (> 430 msec). In addition, any clinically significant findings will be documented in the source documents and later transcribed on to the appropriate eCRF. Each signed original ECG may be reviewed by the responsible site monitor and kept with subject's source documents onsite.

Subjects can have a repeat ECG at any time during the study as warranted, based on the opinion of the Investigator.

**Serum Testosterone Testing**

Blood samples will be collected as indicated in Appendix C to determine serum testosterone concentration. For information on screening serum testosterone, refer to Inclusion Criterion 2.

The average of the Screening Period (SV1, SV2 and SV3 if necessary) testosterone values will be used as the subject's Baseline testosterone value.

After study randomization, pre-dose serum testosterone samples will be collected 24 hours (± 2 hours) of the last applied dose for the purpose of titration. For example, if the last applied dose was at 12:00 pm the day prior to the study visit, the blood sample should be taken between 10:00 am to 2:00 pm.

- Subjects should not apply their regularly scheduled study drug dose prior to the in-person study visits as defined in Appendix C.

- Subjects should receive a reminder to apply the dose 24 hours before the study visit, even if that is not their usual study drug application time.
- The following subjects should be rescheduled within 1 week for a serum testosterone level if their serum testosterone cannot be drawn 24 hours (± 2 hours) from the last applied dose.
  - Subjects who apply a dose less than 22 hours from the time of serum testosterone sample collection.
  - Subjects who apply a dose greater than 26 hours from the time of serum testosterone sample collection.
- Subjects should bring their current study drug to the site. Subjects who forget to bring the study drug to their study visit should make arrangements to return study drug to study site as soon as possible. The dose applied during the study visit will come from the newly dispensed study drug.

Consult Section 5.1 for information on re-screening.

**Clinical Laboratory Tests**

A certified central laboratory will be utilized to process and provide results for the clinical laboratory tests as indicated in Table 3 and collection time points can be found in Appendix C. Unscheduled clinical labs may be obtained at any time during the study if deemed appropriate per Investigator's discretion.

The central laboratory chosen for this study will provide instructions regarding the collection, processing, and shipping of these samples. For study visits when samples for plasma glucose, serum chemistry or testosterone tests are collected, subjects should be fasting (a minimum 8-hour fast) whenever possible. If a subject is not able to fast when necessary, the non-fasting status will be recorded in subject's source document.

Urine samples will be obtained according to Appendix C. The central laboratory will be responsible for performing a macroscopic urinalysis (urine dipstick) on the collected urine specimens. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite,

protein, ketones, or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

The last clinical laboratory test values obtained prior to the first dose of study drug will serve as the Baseline laboratory test values.

**Table 3. Clinical Laboratory Tests**

| **Hematology** | **Clinical Chemistry[a]** | **Urinalysis[b]** |
|---|---|---|
| Hematocrit (Hct)[c]<br>Hemoglobin (Hgb)[c]<br>Red Blood Cell (RBC)c count<br>White Blood Cell (WBC) count<br>Platelet count (estimate not acceptable)<br>Mean Corpuscular Volume (MCV)[c]<br>Mean Corpuscular Hemoglobin (MCH)[c]<br>Mean Corpuscular Hemoglobin Concentration (MCHC)[c]<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils | Blood Urea Nitrogen (BUN)<br>Creatinine<br>Total bilirubin<br>Albumin<br>Aspartate aminotransferase (AST)<br>Alanine aminotransferase (ALT)<br>Alkaline phosphatase<br>Gamma-glutamyl transferase (GGT)<br>Sodium<br>Potassium<br>Calcium<br>Inorganic phosphate<br>Uric acid<br>Cholesterol<br>LDL-C<br>HDL-C<br>Total protein<br>Glucose<br>Triglycerides<br>Bicarbonate/$CO_2$<br>Chloride | Specific gravity<br>Ketones<br>pH<br>Protein<br>Glucose<br>Blood<br>Leukocytes<br>Nitrites |
| | | **Other Laboratory Tests** |
| | | hsCRP[d]<br>PSA[c]<br>Serum Creatinine[e]<br>Fasting Plasma Glucose[a]<br>HbA1c |
| | | **Sex Steroids[a]** |
| | | Testosterone[c]<br>Free Testosterone[c,f]<br>Dihydrotestosterone (DHT)[c]<br>Estradiol[c] |

a. Minimum 8-hour fast except for SV1.

b. A urine dipstick macroscopic urinalysis will be completed by the central laboratory at all required visits. A microscopic analysis will be performed in the event the dipstick results show leukocytes, nitrite, protein, ketones, or blood greater than negative or glucose greater than normal.

c. Post-baseline results are blinded.

d. hsCRP will only be collected during Screening.

e. Serum creatinine obtained according to Appendix C and will be used to calculate eGFR (central laboratory performing calculations). eGFR assessment (CKD-EPI Equation) will be performed in all men.

f. Free Testosterone only collected at SV2 (or SV3 if necessary) and Month 12 (Year 1).

Starting at Day 1, the Investigator will assess results of laboratory tests for clinical significance and will document the assessment in the source record.

**Blinded Laboratory Results:**

Starting at Day 1, the results for the following labs will be blinded to sites/Investigators in an effort to maintain the study blinding:

- Sex Steroids (Testosterone, DHT, Estradiol, Free Testosterone)
- PSA
- Hgb
- Hct
- RBC, MCV, MCH, MCHC

The Investigator will be notified if a subject has a value for testosterone, PSA, or Hct that requires additional follow-up, repeat assessment of the lab of interest, and/or modification of the study drug dosing regimen.

Testosterone and other sex steroid levels should not be collected outside of the protocol.

**Randomization/Drug Assignment**

All Screening laboratory results must be reviewed, signed, and dated by the Principal Investigator or Sub-investigator prior to the Baseline Visit. Subjects will not be enrolled into the study if laboratory or other Screening result abnormalities are deemed clinically significant by the Principal Investigator or Sub-investigator.

Subjects who meet the eligibility criteria may proceed to randomization via IRT at the Day 1 (Baseline) Visit. Enrolled subjects will keep their unique subject number initially assigned at SV1 throughout the study. An IRT system will randomize subjects to receive either topical testosterone or placebo in a 1:1 ratio. Randomization will be stratified by pre-existing CV disease (Yes/No).

**Study Drug Dispensing, Dosing, and Compliance**

Study drug will be dispensed to subjects beginning at Day 1 (Baseline) and at specified visits as shown in Appendix C. The first dose of study drug will be administered after all other Day 1 (Baseline) procedures are completed.

**Site Endpoint Questionnaire and AESI, AEs Leading to Study Drug Discontinuation, SAEs, and Concomitant Medications**

The site staff will ask the subjects several questions about safety endpoints including CV, prostate, and fracture events (example questions Appendix E) during both in-person and phone visits as indicated in Appendix C. A positive response to any of the site endpoint questions will prompt the completion of a more detailed Endpoint Form. The site staff will also collect any AESI, AEs leading to study drug discontinuation, SAEs and concomitant medications at these visits. These questions will be asked of all subjects in the study, both subjects continuing on study drug as well as subjects who prematurely discontinue study drug.

**Rating Scales**

**International Prostate Symptom Score-1 (I-PSS)**

The I-PSS is a questionnaire (example Appendix F) used to help assess urination patterns and define the severity of BPH or lower urinary tract symptoms.[46] The standardized I-PSS instrument will be administered to the subject at designated visits. Subjects will complete the I-PSS as indicated in Appendix C.

**Sexual Function Questionnaires DeRogatis Interview for Sexual Function – Male (DISF – SRII)©**

The DISF-SRII[47] is a brief inventory of questions about sexual thoughts and activity. The questions are divided into 5 sections that ask about different aspects of the individual's sexual experiences. Some questions request answers in terms of "how often" one engages in certain sexual activities. Other questions ask "how intense" one's sexual experiences are. A third type of question asks how much one "enjoyed" or was "satisfied" by different

aspects of sexual activities and relationship. Each section has one or more scale definition boxes located alongside the questions. For Section I of the instrument, the scales range from 0 – 7 or 0 – 5. Results from Section I (Sexual Desire domain) will determine whether or not a subject is included in the sexual function sub-study analysis set. Section I of the DISF-SRII will only be asked at Baseline. Subjects will complete the DISF-SRII Section I as indicated in Appendix C (Main Study) and Appendix O (Sub-study). The example DISF-SRII is provided in Appendix G.

**Hypogonadism Impact of Symptoms Questionnaire (HIS – Q)**

The HIS-Q is a validated patient-reported outcome measurement to evaluate the symptoms of hypogonadism and assess changes in symptoms among men with hypogonadism in response to treatment with TRT. It includes 28 item questions assessing 5 domains (sexual, energy, sleep, cognition and mood) and 2 sexual subdomains (libido and sexual function): sexual domain (5 open ended questions and 7 items spread between the libido and sexual function subdomains), libido subdomain (3 items), sexual function subdomain (4 items), energy domain (3 items), sleep domain (3 items), cognition domain (3 items), and mood domain (7 items).[48] Subjects will complete the HIS-Q as indicated in Appendix C. The example HIS-Q is provided in Appendix H.

**Patient Global Index of Improvement (PGI – I)**

The PGI-I is adapted from questions that assess two other conditions, severity and improvement questionnaires in the treatment of men with lower urinary tract symptoms secondary to BPH,[49] and global impression questionnaires for incontinence.[50] Subjects not participating in either the sexual function or the PDD sub-studies will be asked about their global impression of hypogonadism overall, while men participating in the sexual function sub-study and/or PDD sub-study will be asked about their impression of their libido and/or depression, respectively, since starting study drug. The PGI-I will be completed as indicated in Appendix C (for all subjects in main study) and Appendix O (for subjects who qualify for sexual function and/or PDD sub-studies only). The example PGI-I questions are provided in Appendix I.

**International Index of Erectile Function (IIEF-5) – Sexual Function Sub-Study Only**

The IIEF-5 is a 5-item self-administered questionnaire measurement of erectile dysfunction.[51] Subjects will complete the IIEF-5 questions as indicated in Appendix O. The example IIEF-5 questions are provided in Appendix J.

**Psychosexual Daily Questionnaire (PDQ) Question 4 Only – Sexual Function Sub-Study Only**

The PDQ[52] is a self-reporting instrument designed for the assessment of sexual function and mood on a daily basis. The subjects will be asked to complete Question 4 from the PDQ for 7 consecutive days before each study visit as indicated in Appendix O. The example PDQ Question 4 is provided in Appendix K. If subjects complete less than 4 of 7 days (e.g., Day –7 to Day –1) for the Baseline (Day 1) PDQ assessments, then they will be discontinued from the Sexual Function Sub-Study.

**Patient Health Questionnaire-9 (PHQ-9)**

The PHQ-9 is a validated self-administered questionnaire that is used to evaluate severity of depression. Each of the 9 items in the questionnaire is scored from zero (not at all) to 3 (nearly every day); thus the total score can range from 0 – 27 with higher number denoting greater severity of depression.[53] Subjects will complete the PHQ-9 questionnaire as indicated in Appendix C (SV2) and Appendix O. The example PHQ-9 questions are provided in Appendix L.

**Geriatric Depression Scale (GDS)-15 – PDD Sub-Study Only**

The GDS-15 is a widely used instrument to assess depressive symptoms in older adults. While the instrument was developed and validated for use in older patients, the literature also supports GDS-15 performance characteristics in younger patients.[54] Subjects will complete the GDS-15 questionnaire as indicated in Appendix O. The example GDS-15 questions are provided in Appendix M.

**Additional Depression Questions – PDD Sub-Study Only**

Additional questions will be asked of participants at Baseline to assess their eligibility for the PDD sub-study. Subjects enrolled in the PDD sub-study will complete additional question at the same time points as the GDS-15. The example additional questions are provided in Appendix N.

**Modified Rankin Scale (mRS)**[55]

The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of subjects who have suffered a stroke or transient ischemic attack (TIA) (See Appendix P).

The mRS score will be obtained by interviewing the subject or subject representative when the event is initially reported as well as approximately 90 days following a reported TIA or stroke event to ascertain the level of disability as suggested by the scale. This may be done in person or via the telephone.

**Phone Call**

The subjects will be contacted by phone as indicated in Appendix C. The subjects will be queried about endpoints and AEs following the guidance provided in Section 6.0.

**30-Day Follow-Up Call After Final Visit (FV)**

A 30-day phone call will be performed on all subjects who complete Week 260/FV on study drug. The phone call will check on the status of any AEs (Section 6.1.1) that were ongoing and to determine whether any new AEs have occurred. All events meeting the criteria in Section 6.1.1.1 will be collected. Consult Table 7 for other end-of-study scenarios.

**Final Visit (FV)**

The FV occurs when the subject completes 260 weeks of active treatment or until the primary endpoint is achieved in the study (i.e., the study is stopped). At the FV, all AEs

will be reviewed to determine if the event is resolved, resolved with sequelae, ongoing or fatal.

**Premature Discontinuation (PD) Visit**

The PD Visit (Appendix C) will be conducted when the subject prematurely discontinues from study drug and elects Option 3 or Option 4 (Section 5.4.1). The visit will be scheduled/conducted as close as is feasible to when the subject decides to prematurely discontinue study drug. Subjects requiring PD visits will be followed for safety events outlined in Appendix D and end of study vitality status.

**End of Study (EOS)/Study Completion**

The last contact (e.g., office visit or phone call) with the subject will serve as the EOS for each subject. For subjects completing 260 weeks of treatment on study drug, there will be the 30-day phone call. For subjects prematurely discontinuing study drug less than 30 days before Week 260/FV, then a 30-day phone call will be the EOS. For subjects prematurely discontinuing study drug but continuing study visits greater than 30 days before Week 260/FV, the Week 260/FV will serve as the EOS.

**COVID-19 Pandemic-Related Acceptable Protocol Modifications**

The following modifications are allowed during the COVID-19 pandemic:

Study visits and/or activities should be performed as scheduled whenever possible. Virtual visits are allowed if in-person site visit is not possible due to pandemic related reasons. Screening (SV1, SV2 and SV3), Day 1, Week 2, Week 4, M60/Final and Premature Discontinuation Visits cannot be performed virtually.

During virtual visits, the following activities may be performed:

- Vital signs if able by the subject, weight if able by the subject, AEs/SAEs/AESI and Endpoints collection as well as collection of additional information related to ongoing adverse events.

If a subject missed a visit or had a virtual visit prior to Month 6/Week 26 visit: he should continue using the most recent dose of study drug as per protocol and/or IRT titration notification and complete any missed visits as soon as possible.

If a subject missed or had a virtual Month 3/Week 12 visit: a PSA must be performed at the next in-person visit per protocol, in addition to other laboratory tests.

Subjects who cannot complete an in-person Month 6/Week 26 visit should discontinue study drug temporarily until an in-person visit can occur.

If a subject had a Month 6/Week 26 in-person visit and associated lab tests resulted: he should continue using the most recent dose of study drug as per protocol and/or IRT titration notification and complete any missed visits as soon as possible.

If a subject missed a visit or had a virtual visit after Month 6/Week 26 visit: he should continue using the most recent dose of study drug as per protocol and/or IRT titration notification and complete any missed visits as soon as possible. The physical exam and other missed assessments should be completed at the next in-person visit.

Subjects who did not complete an in-person visit for 12 months should discontinue study drug temporarily until an in-person visit can occur.

### 5.3.2 Safety Variables

#### 5.3.2.1 Primary Outcome Variables

Primary Safety Endpoint: Time to MACE, is defined as time from randomization to first component event occurrence of the composite MACE endpoint. MACE is defined as a composite endpoint consisting of any of the following:

- Nonfatal MI
- Nonfatal stroke
- Death due to CV causes

#### 5.3.2.2 Secondary Safety Variables

This study will examine the effect of testosterone on a number of additional safety endpoints as specified below.

Secondary CV safety endpoint is defined as time from randomization to first component event occurrence of the composite endpoint consisting of the following:

- Nonfatal MI
- Nonfatal stroke
- Death due to CV causes
- Cardiac revascularization procedures/cardiac PCI and CABG

Secondary Prostate Safety Endpoints:

- High grade prostate cancer (Gleason score of 4 + 3 or higher)

#### 5.3.2.3 Tertiary Safety Endpoints and Tertiary Prostate Endpoints

Tertiary Safety Endpoints:

- All-cause mortality
- Heart failure events (hospitalization or urgent visit)
- Venous thromboembolic events to include DVT/PE/venous thromboembolism (excluding superficial thrombophlebitis)
- Peripheral arterial revascularization

Tertiary Prostate Safety Endpoints:

- Prostate biopsy
- Any prostate cancer
- Acute urinary retention
- Starting pharmacologic treatment for lower urinary tract symptoms

- Invasive prostate surgical procedures (e.g., prostatectomy, transurethral prostate resection, brachytherapy or other prostate surgical procedure) for benign prostatic hyperplasia

#### 5.3.2.4 Adjudicated Events

The CEC will adjudicate pre-specified CV, prostate and fracture events during the study, as described in Appendix D. The CEC will have separate charters for each of the three event categories governing the adjudication progress.

Many of the endpoint events from this study will be reviewed by experts serving on the adjudication committees to ensure the accuracy of the data. Adjudication results for these endpoint events will be for research purposes only and will not be used for the clinical management of subjects. Therefore, adjudication results will not be shared with the Investigators.

### 5.3.3 Efficacy Variables

A limited number of pre-specified efficacy endpoints have been included as secondary outcomes in five efficacy domains.

The following efficacy endpoints will be evaluated in sub-studies or analyses of subpopulations:

1. Improvement in sexual activity in hypogonadal men with low libido
2. Remission of depression in hypogonadal men with late-onset, low grade PDD (dysthymia)
3. Reduction in incidence of clinical fractures
4. Correction of anemia in subset of subjects with Baseline anemia
5. Reduction in progression from pre-diabetes to diabetes in subset of subjects with pre-diabetes at Baseline

For additional efficacy sub-study information, refer to Appendix O.

## 5.4 Removal of Subjects from Therapy or Assessment

### 5.4.1 Discontinuation of Individual Subjects

Each subject has the right to discontinue from the study or the study drug at any time. In addition, the Investigator may discontinue a subject from the study drug at any time. Subjects who discontinue study drug after they have been randomized will not be replaced.

***Temporary Discontinuation of Study Drug***

Subjects who have received marketed testosterone replacement therapy should be managed per Section 5.2.3.1.

If a subject temporarily discontinues study drug, every attempt should be made to restart study drug as soon as possible when medically appropriate based on the Investigator's judgment, provided the subject does not meet any of the reasons for permanent discontinuation of study drug as listed below. There will be no minimum or maximum allowed duration of study drug discontinuation, and the regularly scheduled visits and/or phone calls should continue while the subject is not on study drug. Subjects eligible to restart study drug should restart study drug based on their last study prescribed dose.

If study drug is discontinued for ≤ 4 weeks, no further action is necessary. If study drug is discontinued for > 4 weeks, subject should return for an unscheduled visit 4 ± 1 weeks after restarting study drug to assess his testosterone level.

The dates of study drug discontinuation and when drug is restarted, and the reason for temporary discontinuation should be documented in the source document and eCRF.

Once study drug is restarted, the subject should return for the next closest scheduled visit (if study visit(s) were missed) and complete all study visit assessments.

***COVID-19 Pandemic-Related Acceptable Protocol Modification***

During the COVID-19 pandemic, it is necessary to employ mitigation strategies to enable the Investigator to ensure subject safety and continuity of care.

The Investigator should contact the Retention Hotline before discontinuing a subject from the study drug or study for any reason to ensure all acceptable mitigation steps have been explored.

***Permanent Discontinuation of Study Drug***

In rare instances, it may be necessary for a subject to permanently discontinue study drug. Permanent study drug discontinuation is clearly justified by meeting the protocol criteria for permanent discontinuation as described below. Once the subject discontinues study drug, the appropriate study visits and/or phone calls should still be continued until the study ends.

**Reasons for Permanent Study Drug Discontinuation**

Subjects should discontinue study drug for any of the following:

- Confirmed serum testosterone levels > 750 ng/dL even after down-titration to the lowest dose (see Section 6.1.9)
- Confirmed prostate cancer diagnosis during the study (see Section 6.1.8)
- Confirmed repeat Hct value > 54% even after down titration to the lowest dose (see Section 6.1.9)
- PDD sub-study: Subjects at risk of suicide as determined by the Investigator and/or a non-zero response to Question 9 on post-Baseline PHQ-9 (Appendix L)

***Discontinuing the Study Entirely (Withdrawal of Informed Consent)***

In order to minimize missing data for safety and efficacy assessments, subjects who discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless they have decided to discontinue their study participation entirely

(withdrawal of informed consent). If a subject discontinues the study prematurely, the subject should undergo a PD Visit at the time he discontinues from the study regardless of when he discontinued study drug. Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug. The subjects should also be informed of their options for continued study visits and/or follow-up phone calls.

Discontinuation of study drug should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for indirect follow-up, e.g., medical records checks. If the subjects decide to discontinue the study entirely, the subjects should be asked if other means of follow-up are possible, e.g., medical records check. Subjects requesting withdrawal should be advised that withdrawal of informed consent to continue in the study will diminish the public health value of the study. Withdrawal of informed consent for follow-up should be accompanied by documentation of the reason for withdrawal.

Subjects who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented.

Preferably, the subject should withdraw consent in writing and, if the subject or the subject's representative refuses or is physically unavailable, the site should document the reason for the subject's failure to withdraw consent in writing. While subjects have the right to discontinue study drug and leave the study at any time, Investigators and site staff will ask the subjects to remain in the study, if they are able, for follow-up evaluations.

**Retention Hotline and Continued Participation Options**

Investigator(s) or designee should contact the Retention Hotline prior to the subject permanently discontinuing from the study drug or the study entirely (withdrawal of informed consent) in order to discuss the subject's status and ensure continued follow-up in the study. For all subjects who inform the site that they want to discontinue the study

permanently (withdrawal of informed consent), the study site must discuss with the subject the options available for continued participation.

As a last resort, in an effort to optimize subject retention, the following four options should be offered to the subject regarding continued participation; however, every effort should be made to keep subjects who discontinue study drug under participation Option 1, matching the same study visits and procedures as subjects who remain on study drug.

**Option 1:** Subject discontinues study drug temporarily or permanently but continues to participate in study site visits and procedures following the protocol specified visit schedule until the end of the study.

**Option 2:** Subject discontinues study drug and study procedures permanently but continues telephone (or other communication, i.e., email or text messages as allowed according to institutional guidelines) contact following the protocol specified visit schedule until the end of the study. Date of the contact, the identity of the contact, update contact information, concomitant medications, and SAE assessments including but not limited to identification of AESI and MACE should be collected at each telephone visit (or other communication). All events meeting the criteria in Section 6.1.1.1 will be collected.

**Option 3:** Subject discontinues study drug and study procedures permanently and does not allow site to contact him but allows the site to review the subject's medical records and/or contact their Primary Care Physician and/or Designated Contact following the protocol specified visit schedule or at least every 6 months until the end of the study, to ensure his safety, and to check if the subject had any AESI, SAEs, and identification of MACE. At the time that the subject discontinues from the study, the subject should undergo a FV. The reason for discontinuation should be collected and recorded on the CRF. Date of the contact or review of the records, the identity of the contact or source, and any updates to concomitant medications and SAE assessments including but not limited to identification of AESI and MACE (if available) should be collected at each

contact/review of medical records. All events meeting the criteria in Section 6.1.1.1 will be collected.

**Option 4:** Subject discontinues study drug and study procedures permanently and chooses no further contact from the site and withdraws informed consent. Subject revokes consent to contact him directly or his Primary Care Physician and/or Designated Contact or review of his medical records. Vital status will be checked at the end of study using appropriate available public information sources, if allowed according to institutional guidelines. Whenever possible, all events meeting the criteria in Section 6.1.1.1 will be collected.

NOTE: Options 2 – 4 should not be explored if the subject is willing to continue participation under Option 1. Site should make every effort to maintain in-person visits wherever and whenever possible as defined in Appendix C.

The subject's continued level of participation should be clearly documented and updated in the subject's source documents and eCRFs. If a subject no longer wishes any further contact, the primary criterion for withdrawal of consent must also be recorded. In addition, efforts should be made to perform all assessments for the PD Visit.

***Lost to Follow-Up (LTFU)***

Subjects may become potentially LTFU at any time during the study, especially after missed study visits. The status of LTFU is defined by the inability to gather vital status at the end of the study and only when instructed to do so by the study team. Every effort will be made to ensure that the subject continues to return to the clinic for study visits and avoid LTFU during the conduct of the study. After the first missed visit, subjects that are potentially LTFU should receive a minimum of three documented phone calls, faxes, and/or emails as well as one registered/certified mail letter. Additional attempts to contact the subject should be performed following the study specified visit schedule until the study is completed. All reasonable efforts must be made to locate subject to determine

and report his ongoing status. This includes follow up with persons authorized by the subject. All attempts should be documented in the subject's source documents.

The Investigator must attempt to document assessments of study endpoints and occurrence of events through the end of the study. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death as well as obtain records to support this through the subject's next of kin. If the subject died at a medical facility or hospice, records should be obtained from the facility or the provider that referred the subject to hospice. If the subject died at home, the site should document the known circumstances that preceded the death. If medical records are not available, the site will be asked to provide a written narrative. Per the adjudication charter, undetermined deaths will be adjudicated as CV deaths through the adjudication process.

If the use of a third-party representative (a patient locator service) to assist in the treatment portion of the study has been included in the subject's informed consent, then the third-party representative may work with the site staff to obtain the subject's contact information or other public vital status data necessary to complete the treatment portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains LTFU at the end of the study, then the last known alive date, as determined by the Investigator, should be reported and documented in the subject's source documents.

**Vital Status Assessment at EOS**

At the end of the study, the Investigator should attempt to obtain vital status and primary CV safety endpoint information (CV death, non-fatal MI, non-fatal stroke) for those subjects not completing all study required visits (e.g., LTFU or withdraw consent if agreed to by the subject).

### 5.4.2 Discontinuation of Entire Study

The Sponsor may terminate this study prematurely in its entirety or AbbVie may terminate this study prematurely at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The Investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, AbbVie, or its designee, will immediately notify the Investigator by telephone and subsequently provide written instructions for study termination.

When the study ends or is terminated, all randomized subjects continuing in the study will return for the FV procedures as specified in Appendix C Study Activities. For subjects remaining on study drug, the post-therapy SAE collection period will continue for 30 days following the termination of study drug therapy.

## 5.5 Treatments

### 5.5.1 Treatments Administered

Though all subjects will start on the 40.5 mg dose (2 pump actuations) of the study drug once daily, they may receive a dose in the range of 20.25 mg (1 actuation) to 101.25 mg (5 actuations) in 20.25 mg increments during the course of the study if titrations are necessary.

Before using a new pump of study drug, the pump will need to be primed by pushing the actuator all the way down 3 times. Do not use any study drug that came out while priming the pump. Wash it down the sink to avoid accidental exposure to others. The pump only needs to be primed when using a new pump for the first time. For the first study drug administration at Baseline, the subject should administer the study drug at the site so that the site staff can observe the administration of study drug.

The subject will self-administer study drug once daily in the morning to the shoulder(s) and upper arm(s). On subsequent study visit days, subjects should not apply their daily

dose until after a sample is collected to measure serum testosterone (See Appendix C for titration study visits). Following sample collection, subjects are to apply study drug at the site. Subjects should be rescheduled within 1 week for a serum testosterone level if their serum testosterone cannot be drawn 24 hours (± 2 hours) from last applied dose.

The study drug should not be administered to other parts of the body, including abdomen, genitals, chest, armpits (axillae), or knees.

**Figure 1. Application Sites**

Following study drug administration, the subjects should wash their hands with soap and water. After the study drug has completely dried, the subject should cover up the application site with a t-shirt.

### 5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 4.

**Table 4. Identity of Investigational Product**

| Investigational Product | Mode of Administration | Formulation | Strength per Actuation | Manufacturer |
|---|---|---|---|---|
| AndroGel 1.62% | Topical | Gel | 20.25 mg of testosterone per 1.25 g of gel | Laboratoires Besins-International |
| AndroGel 1.62% matching placebo | Topical | Gel | NA | Laboratoires Besins-International |

#### 5.5.2.1 Packaging and Labeling

The study drug will be provided in metered dose pumps containing AndroGel 1.62% or matching placebo. Each pump will be labeled as required per US requirement. Labels must remain affixed to the containers. The approximate dosage and duration for one bottle are depicted in Table 5.

**COVID-19 Pandemic-Related Acceptable Protocol Modifications**

If a subject is unable to come to the study site to pick up his study drug due to COVID-19, a direct-to-patient (DTP) study drug shipment can be made from the study site to the subject and/or return of study drug to study site by courier if allowed by local regulations. Each study site is responsible for obtaining any necessary approval for providing DTP study drug shipment from any applicable state or federal agency.

Study drug may be shipped from the study site directly to the study subject's home if all the following criteria are met:

- DTP shipment of study drug is allowed by local regulations and the relevant IRB/IEC.
- Subject agrees to have the study drug shipped directly to his home.

Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary. Shipments of study drugs from the study site to a subject's home will be

appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; however, due to COVID-19 related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the study site. Also, Marken is able to pick-up study drug from a study subject's home and return it to the study site.

- If study sites are not able to use Marken, then another courier may be acceptable. Any study site that uses another such courier must follow the controlled substance courier requirements and be responsible for complying with any applicable laws and regulations related to the shipping to and from the site of a controlled substance.

In each instance, the study site will work directly with Marken or another courier to facilitate the DTP shipment. As such, AbbVie should not receive subject identifying information related to these shipments.

The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug, and for obtaining consent to provide delivery information to the courier and documenting this consent in source documents.

**Table 5. Approximate Dosage and Duration of Use for 1 Bottle of Study Drug**

| Dosage | Duration of Use for 1 Bottle |
|---|---|
| 20.25 mg (1 actuation) | 60 days |
| 40.5 mg (2 actuations) | 30 days |
| 60.75 mg (3 actuations) | 20 days |
| 81.0 mg (4 actuations) | 15 days |
| 101.25 mg (5 actuations) | 12 days |

#### 5.5.2.2 Storage and Disposition of Study Drugs

All clinical drug supplies are to be stored in a secure, monitored, limited-access area in accordance with labeled storage conditions. The study drug should be stored between 15°

to 25°C (59° to 77°F). The Investigator will maintain accurate records of the disposition of all clinical drug supplies received during the study. The controlled storage area should have a temperature recording device capable of recording the high and low temperatures in a 24-hour period. A storage temperature log is to be maintained to document proper storage conditions. The temperature must be recorded on a temperature log every business day. Malfunctions or any temperature excursions must be reported to AbbVie immediately. In case of a temperature excursion, study drug should be quarantined and not dispensed until AbbVie deems the study drug as acceptable.

AndroGel 1.62% is listed as Drug Enforcement Administration (DEA) CIII drugs in the US and must be handled according to applicable federal and local regulations.

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to AbbVie.

### 5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects will be randomized using IRT. Before the study is initiated, IRT directions will be provided to each site.

For subjects that re-screen, the Screening number assigned by IRT at the initial Screening visit should be used; a new Screening number should not be requested. Subjects will keep the same subject number assigned to them at Screening.

Subjects who are eligible (Section 5.2) will be randomized in a 1:1 ratio to one of two treatment groups (Table 4) and stratified by pre-existing CV disease (Section 8.3).

Blinded study drug will be dispensed on Day 1 (Baseline) and at regular intervals thereafter during the treatment period according to Appendix C. At the designated scheduled study visits, subjects will return to the site to obtain new supply of study drug and return used/unused study drug packaging supply. The unused study drug returned by

the subject will not be re-dispensed. The Investigator or designee will access the IRT system at each study visit prior to dispensing study drug to the subject. Study drug cannot be dispensed without using the IRT system. Study containers will be labeled with their unique module number.

### 5.5.4 Selection and Timing of Dose for Each Subject

Selection of the dose for this study is discussed in Section 5.6.4.

All eligible subjects will be started at 40.5 mg of study drug, either active drug or placebo, on Study Day 1 (Baseline). Titration will be based on pre-dose morning total serum testosterone concentrations and will be communicated to the sites via an IRT system, while maintaining blinding of the actual testosterone values.

Subjects will return for pre-dose serum testosterone assessment 24 hours (± 2 hours) after the last applied dose according to the titration study visit schedule in Appendix C.

Subjects will be asked when they last applied study drug. Subjects should be rescheduled within 1 week for a serum testosterone level if their serum testosterone cannot be drawn 24 hours (± 2 hours) from the last applied dose.

Within approximately 7 days of these titration study visits, the subject's dose may be titrated up or down in 20.25 mg increments or remain on the previously assigned dose, based on pre-specified criteria (Table 6).

No dose can be titrated below 20.25 mg or above 101.25 mg during the course of the study.

The pre-specified titration criteria to be applied during the study are based on testosterone serum concentrations as shown in Table 6.

**Table 6. Dose Titrations**

| Pre-Dose (Preferably Morning) Sample Collection for Serum Testosterone Concentrations to Occur Within 24 Hours (± 2 hours) Following the Last Applied Dose | Dose Titration |
|---|---|
| Greater than 750 ng/dL | Decrease daily dose by 20.25 mg (one pump actuation) |
| Between 350 ng/dL and 750 ng/dL, inclusive | No change: continue on current dose |
| Less than 350 ng/dL | Increase daily dose by 20.25 mg (one pump actuation) |
| Irrespective of testosterone levels, subjects randomized to placebo will receive sham titrations | Dose titrations will be performed at periodic intervals for subjects randomized to placebo |

Subjects may also have study drug titrated for elevated Hct (Section 6.1.9).

If subjects are asked to titrate following a titration visit, they will be asked to cross out the previous instructions specifying their previous number(s) of pumps/actuations per day or dose and fill in their updated number of pumps/actuations per day or dose.

Should a subject's dose require titration, site personnel will communicate this to the subjects within approximately 3 days from the receipt of IRT notification to titrate. Serum testosterone levels for visits after Screening will remain blinded to the subjects and site personnel.

If subjects are not taking their prescribed dose (e.g., titration was required but subjects did not titrate and continued on the non-titrated dose from the previous visit/testosterone blood draw), the site should not draw a serum testosterone. The subject should be instructed to start their prescribed dose and return to the site for an unscheduled visit in 4 ± 1 weeks for a testosterone blood draw in order to determine if titration is needed.

### 5.5.5 Blinding

Study drug (active and placebo) will be supplied in a blinded fashion.

Throughout the course of the study, the subject, all study site personnel and the Sponsor will be blinded to each subject's treatment.

Central third party vendors (IRT and central laboratory) will be unblinded to serum testosterone levels and will coordinate titrations for active treatment and placebo, as well as any actions necessary as a result of sustained high testosterone levels despite down-titration or as a result of increased Hct.

The blind for an individual subject may be broken using IRT system if, in the opinion of the Investigator, it is in the subject's best interest to do so. The Investigator must make every effort to contact AbbVie or designee before breaking the blind. AbbVie or designee must be notified within 24 hours of the blind being broken. The date, time, and reason the blind was broken must be recorded on the appropriate eCRF. In the highly unlikely event that unblinding is necessary for a subject, only a designated AbbVie staff member outside of the study team will be unblinded. All other personnel involved with the conduct of the study, including the CEC, will remain blinded. Once the blind has been broken for an individual subject, the subject will discontinue study drug but the subject may remain in the study for regularly scheduled visits.

#### 5.5.5.1 Blinding of Data for Independent Data Monitoring Committee (DMC)

An external independent DMC comprised of persons, independent of the Sponsor, the Clinical Research Organization (CRO), and the Academic Research Organization (ARO), with relevant expertise in their field will review unblinded safety data from the ongoing study. The primary responsibility of the independent DMC will be to protect the safety of subjects participating in this study.

A separate independent DMC charter will be prepared outside of the protocol and will describe the roles and responsibilities of the independent DMC members, frequency of data reviews, and relevant safety data to be assessed.

#### 5.5.5.2 Blinding of Data for Executive Steering Committee (ESC)

A separate charter will be prepared for other governance body (ESC) outside of the protocol to define the roles and responsibilities.

The CECs will not be responsible for any safety assessment of the study. The responsibility for safety assessment will remain with the DMC, which will act independently from the Sponsor, ESC, and CECs.

### 5.5.6 Treatment Compliance

Subjects will be instructed to return all used or unused bottles at each visit to determine compliance via bottle weight.

At each of the visits, the study coordinator will question the subject regarding adherence to the assigned regimens. A weight measurement of the study drug pump bottle will be conducted. Study drug lot number, the date that the study drug bottle(s) were dispensed/returned and the weight of the returned study drug bottles will be recorded.

The bottle weight of the returned study drug bottles will be compared to an average bottle weight to determine compliance. The number of doses that should have occurred between visits will be calculated.

Subjects with compliance values below 80% or above 120% compliance will be re-instructed on proper use and informed of the importance of compliance to continue in the study.

An overall accountability of study drug will be performed and verified by AbbVie/designee.

### 5.5.7 Study Drug Accountability

The Investigator must agree to comply with all applicable DEA laws and regulations regarding controlled substances as outlined in 21 CFR 1300. Additionally, the Investigator must agree to limit access to the study drug only to the named

Sub-investigators or to other appropriately designated study personnel or monitoring personnel. Study drug will only be dispensed to subjects enrolled in the study by the Investigator or his/her designated representatives.

Study drug will only be shipped once the DEA License has been received from each site. The study drug must be shipped to the address listed on the Form DEA-223. Study drug must be securely stored at the same location according to DEA guidelines for CIII controlled substances. Upon receipt of a shipment, the Investigator or site representative at the site will 1) open and inspect the shipment; 2) verify that the study drug supplies have been received intact, in the correct amounts and at the correct address; 3) acknowledge receipt of study drug consignment via the IRT system.

The IRT system will maintain a current and accurate inventory of all study drug, accountability, reconciliation, returns and destruction for each site. The investigational site will weigh returned opened study drug and enter the weight into the IRT system. Study drug bottles that are returned unopened at a visit will not be weighted but they must be reconciled.

Subjects should return all used and unused study drug at each visit. Study drug accountability will be recorded in IRT and compliance will be performed by the site staff in a timely manner so that the subject can be counseled if compliance is outside of the accepted range (i.e., below 80% or above 120%). The monitor will confirm and verify ongoing study drug accountability.

Upon completion of the study, the investigational site must complete a final inventory of supplies. All original study drug bottles supplied by AbbVie, whether empty or containing unused drug, must be inventoried and returned to AbbVie or an AbbVie designated site for destruction. Return shipping labels must be attached to the containers. The monitor will generate and prepare a shipment for destruction within the IRT system.

## 5.6 Discussion and Justification of Study Design

### 5.6.1 Discussion of Study Design and Choice of Control Groups

A placebo-controlled study is one way to assess whether or not TRT significantly impacts the risk of CV events. Use of CECs and a DMC, both composed of independent experts, to maximize the unbiased and consistent adjudication of events, and for ongoing evaluation of safety are well-established components of ethical, well-run clinical studies designed to assess CV outcomes.

### 5.6.2 Appropriateness of Measurements

In this CVOT, the incidence of MACE in symptomatic, hypogonadal men at increased CV risk will be ascertained. Specifically, the incidence of nonfatal MI, nonfatal stroke and CV death (including fatal MI and fatal stroke) will be measured in both the active and placebo groups as the primary endpoint of study.

Additionally, efficacy endpoints based on pre-specified hypotheses will be assessed as secondary outcomes in several efficacy domains. These secondary endpoints are consistent with symptom domains and/or target organ systems that have demonstrated some level of responsiveness in past TRT studies and will allow the testing of specific efficacy hypotheses in five efficacy domains: improved sexual activity and function in middle-aged and older hypogonadal men with low libido; remission of depression in men with low grade PDD (dysthymia); slowing progression to diabetes in men with pre-diabetes; correction of anemia in men with anemia; and reduction of clinical bone fracture.

Specified laboratory serum testosterone assessments will be used as a measure of adequate titration of study drug; standard clinical and laboratory procedures will be utilized in this study.

### 5.6.3 Suitability of Subject Population

This study will enroll hypogonadal men at increased risk for CV events. Eligible subjects are men between the ages of 45 and 80 years who have low serum testosterone, signs or symptoms that are associated with hypogonadism, and who may benefit from therapeutic intervention by raising and maintaining their testosterone concentrations within the normal range. Confirmation of testosterone values below normal limits will be conducted during Screening. Subjects who are not suitable for long-term placebo therapy, such as men with clear organic and/or genetic etiology, or hypogonadal men with two screening testosterone levels < 100 ng/dL, for whom long-term therapy with placebo might not be medically appropriate, will be excluded. Subjects will either be naïve to testosterone therapy or have not been treated with testosterone in the past 6 months. Men for whom there are a relative or a concrete contraindication for testosterone therapy such as those with history of prostate or breast cancer, severe lower urinary tract symptoms, erythrocytosis, and those seeking fertility will be excluded.

The eligibility criteria will ensure the enrollment of subjects who are experiencing signs/symptoms that may be associated with low testosterone and are at risk of experiencing a CV outcome event during the study. The study will also allow for the evaluation of the effect of TRT on the incidence of MACE in hypogonadal men with increased risk for CV events within a reasonable time period. Likewise, the study will assess whether testosterone replacement beneficially impacts a pre-specified set of efficacy outcomes.

### 5.6.4 Selection of Doses in the Study

With the exception of the 101.25 mg dose, all doses utilized in the study are per the product label of AndroGel 1.62%. The maximum dose of 101.25 mg dose was selected to ensure that men not achieving normal testosterone levels at the highest labeled dose have the opportunity to optimize their testosterone levels. Though not pursued in the development program for AndroGel 1.62%, AbbVie does have data characterizing the pharmacokinetics of the 101.25 mg dose (data on file).

# 6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The study drug contains:

- AndroGel 1.62% or matching placebo
- Pre-filled bottle with actuator

Complaints associated with any component of study drug must be reported to AbbVie. For AEs related to any component of study drug, please refer to Sections 6.1 through 6.1.5. For Product Complaints, please refer to Section 6.2.

## 6.1 Medical Complaints

The Investigator will monitor each subject for clinical and laboratory evidence of AESI, AEs leading to study drug discontinuation, and SAEs, on a routine basis throughout the study. The Investigator will assess and record these events in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the AE to study drug, and any action(s) taken (e.g., interruption of study drug). For SAEs considered as having "no reasonable possibility" of being associated with study drug, the Investigator will provide an "other" cause of the event. For AEs to be considered intermittent, the events must be of similar nature and severity. AEs as defined above, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All AESI, AEs leading to study drug discontinuation and SAEs should be followed until resolution or marked as ongoing if the study is completed and the event is still pending resolution.

### 6.1.1 Definitions

#### 6.1.1.1 Adverse Event

AEs will not be collected in the study unless they meet the definition of an AESI, they resulted in study drug discontinuation or they met regulatory criteria for SAEs as outlined in Section 6.1.1.3.

Adverse events of cancers should be reported per protocol defined criteria and recorded on the AE/SAE form along with Cancer Diagnosis Study form in EDC.

Primary and secondary endpoints that are SAEs will be collected but will be considered expected for the purposes of FDA Investigational New Drug (IND) safety expedited reporting. Therefore, they will be exempt from FDA IND individual case safety reporting. See Appendix D for the list of these endpoints.

An elective surgery/procedure scheduled to occur during the study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an SAE.

#### 6.1.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to AbbVie as an SAE within 24 hours of the site being made aware of the SAE.

| | |
|---|---|
| **Death of Subject** | An event that results in the death of a subject. |
| **Life-Threatening** | An event that, in the opinion of the Investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form. |

| | |
|---|---|
| **Hospitalization or Prolongation of Hospitalization** | An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility. |
| **Congenital Anomaly** | An anomaly detected at or after birth, or any anomaly that results in fetal loss. |
| **Persistent or Significant Disability/Incapacity** | An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle). |
| **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome** | An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. |

For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate CRF.

#### 6.1.1.3 Adverse Events of Special Interest (AESI), AEs Leading to Study Drug Discontinuation and Serious Adverse Events (SAEs)

Along with any AEs leading to study drug discontinuation and SAEs, the Investigator will monitor each subject for pre-defined AESI throughout the study. See Appendix D for a detailed list of AESI.

### 6.1.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each AE:

| | |
|---|---|
| **Mild** | The AE is transient and easily tolerated by the subject. |
| **Moderate** | The AE causes the subject discomfort and interrupts the subject's usual activities. |
| **Severe** | The AE causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening. |

### 6.1.3 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

| | |
|---|---|
| **Reasonable Possibility** | After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information) to suggest a causal relationship. |
| **No Reasonable Possibility** | After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **insufficient** evidence (information) to suggest a causal relationship. |

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated."

In addition, when the Investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an Investigator's opinion of no reasonable possibility of being related to study drug is given, an alternative etiology or cause of event must be provided by the Investigator for the SAE.

### 6.1.4 Adverse Event Collection Period

All defined AEs (Section 6.1.1.1 through Section 6.1.1.3) will be recorded from the time of study drug administration until the end of the study/study completion.

All AESI, AEs leading to study drug discontinuation and SAEs will be followed until resolution or achievement of a new stable state, or until the subject withdraws consent for study participation, or until the final study-related communication (e.g., phone call at the end of the study or 30 days after last dose as define above or final study communication in subjects truly LTFU), whichever occurs first.

In addition, SAEs will be collected from the time the subject signed the study-specific informed consent.

Subjects who discontinue the study drug without withdrawing consent will be followed for AEs for the duration of the study. Subjects discontinuing study drug at or near the end of the FV will be contacted up to or including 30 days later.

Regardless of the below scenarios, every effort will be made to obtain vital status and complete Endpoint information prior to database lock as described in Appendix E.

**Table 7. End of Study (EOS) Scenarios**

| Scenario | Last Visit Type | 30-Day Follow-Up Phone Call |
|---|---|---|
| Completes Week 260/FV on study drug | Final Visit | Yes |
| Option 1 (Section 5.4.1): Discontinues study drug but follows protocol specified visits and procedures | Final Visit | No* |
| Option 2 (Section 5.4.1): Discontinues study drug but allows phone contact | Phone call as Final Visit if in person visit is not possible | No* |
| Option 3 (Section 5.4.1): Discontinues study drug/study procedures but allows medical record review | Premature Discontinuation Visit | N/A** |
| Option 4 (Section 5.4.1): Withdraws informed consent | Premature Discontinuation Visit | N/A*** |

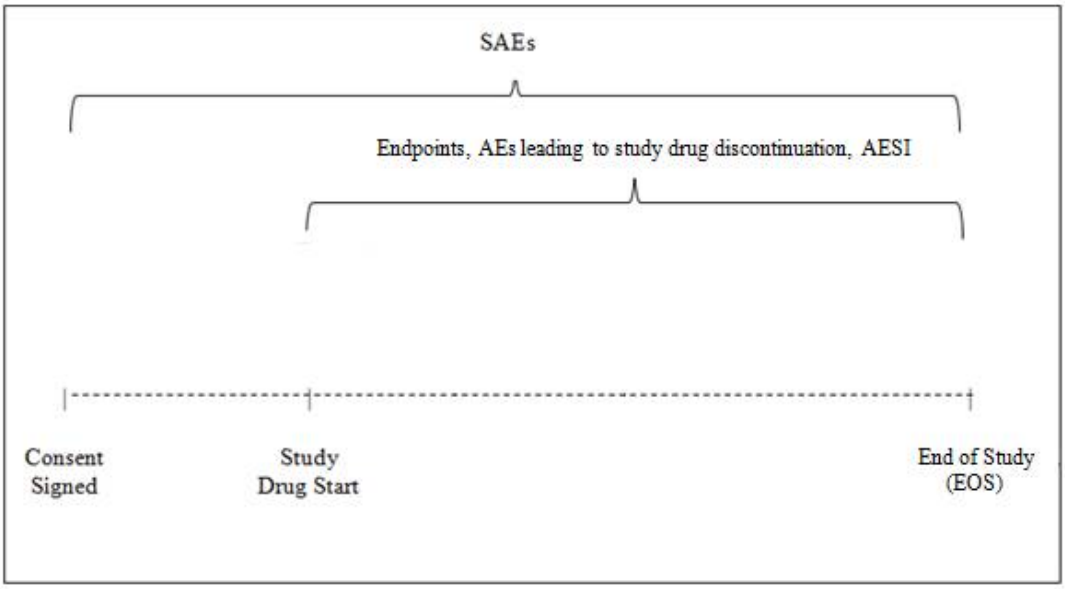
* If subject discontinues study drug within 30 days of Week 260/FV, subject should receive a 30-day phone call.

** This scenario assumes that the subject does not want further phone contact. If there is access to medical records, every attempt should be made to obtain primary safety endpoint information (i.e., CV death, nonfatal MI, nonfatal stroke). Any updates to concomitant medications and SAE assessments including but not limited to identification of AESI and MACE (if available) should be collected.

*** This scenario assumes that the subject does not want further phone contact. Will attempt to obtain vital status at EOS.

AE information will be collected as shown in Figure 2.

**Figure 2. Adverse Event Collection**




Throughout treatment, AESI, AEs leading to study drug discontinuation and SAEs will be collected utilizing standard eCRFs and will be reported via the electronic data capture (EDC) system.

**COVID-19 Pandemic-Related AE/Discontinuations Reporting Requirements**

**'COVID-19 infection'** should be documented for all COVID-19 related AEs on the AE eCRF page in EDC.

Discontinuation due to COVID-19 related AE should be documented if subject permanently discontinues study drug (or study) or has a study drug interruption, COVID-19 AE should be noted as the reason on the applicable eCRF form.

- On the Endpoint form/documentation for MACE, indicate if the event is due to COVID-19 by adding in '**COVID-19 infection**.'
- If subject permanently discontinues study drug (or study) or has a study drug interruption due to risk of COVID-19 that is not considered an AE, document

**'COVID-19 logistical restrictions'** as the reason on the applicable eCRF or IRT forms.

### 6.1.5 Adverse Event Reporting

In the event of an SAE whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the EDC system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

**Email: PPDINDPharmacovigilance@abbvie.com**

**FAX to: +1 (847) 938-0660**

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director (TA MD):

[redacted] MD
1 North Waukegan Road
AP31-1
North Chicago, IL 60064

Telephone Contact Information:
Office:
Mobile:
Email:

In emergency situations involving study subjects when the primary TA MD is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

**Phone: +1 (973) 784-6402**

### 6.1.6 Pregnancy

Pregnancy of the subject's female partner will be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Information regarding pregnancies in the partners of study subjects will be collected from the date of first dose through 30 days following the last dose of study drug.

Information regarding a pregnancy occurrence in a study subject's partner and the outcome of the pregnancy will be collected. In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information.

The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, is considered an SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

### 6.1.7 Management of Abnormal Laboratory Results (PSA, Hct, and Testosterone)

Testosterone, PSA and Hct values remain blinded throughout the study starting at Day 1. Elevated PSA, Hct and serum testosterone values meeting the criteria in Section 6.1.8 and Section 6.1.9, respectively, will require additional action. For elevated PSA values, the central laboratory will communicate to the site via lab report the need for further action; for elevated Hct and serum testosterone, the IRT system will communicate to the site via IRT notification the need for further action.

### 6.1.8 Elevated Prostate Specific Antigen Management

All PSA values will be blinded starting at Day 1. As referenced in Section 6.1.7, for elevated values, the central laboratory will notify the site via lab report. The site should schedule a repeat PSA approximately 4 – 6 weeks after the initial test.

Subjects should also be made aware that long plane or car rides, ejaculation, bike riding, urinary tract infections (UTIs), recent catheterizations, prostatitis are examples of factors that can affect PSA levels. Subjects who need a repeat PSA should be encouraged to abstain from activities that are known or suspected to increase PSA for the 48 hours prior to the repeat PSA.

The Investigator will be notified of the elevation and will refer the subject to a urologist for further evaluation. It is recommended to continue study drug in these subjects while being evaluated by a urologist. Subjects with non-confirmatory findings (e.g., negative biopsy, decision on the urologist's part not to do additional investigations) following the evaluation may continue on study drug. Subjects with biopsies positive for prostate cancer should have study drug discontinued (Section 5.4.1).

A subject will be referred for urological evaluation for consideration of further work-up, which may include a prostate biopsy, if a new prostate nodule or induration is detected, or if he meets any of the following criteria:

| **Elevated PSA criteria** | | |
|---|---|---|
| | **Subjects NOT taking 5-ARI** | **Subjects TAKING 5-ARI** |
| Confirmed PSA increase above Baseline value during the first year | PSA > 1.4 ng/mL above baseline | PSA > 0.7 ng/mL above baseline |
| Confirmed absolute PSA value at any time during the study | PSA > 4.0 ng/mL | PSA > 2.0 ng/mL |
| Men 45 – 54 years of age | Baseline PSA was < 1.5 ng/mL and whose PSA increases to > 3.0 ng/mL | Baseline PSA was < 0.75 ng/mL and whose PSA increases to > 1.5 ng/mL |

For men age 55 or older whose repeat PSA confirms the 1.4 ng/mL (0.7 ng/mL in men on 5-ARI) increase or a level > 4.0 ng/mL (> 2.0 ng/mL in men on 5-ARI), their risk variables will be entered into the PCPT Risk Calculator Version 2.0.[56] The three resulting estimates will be provided: Risk of no cancer, risk of low-grade cancer, risk of high-grade cancer. These results will be calculated and provided to the subject. With the subject's own risk estimates, he may then be shown an IRB approved video that provides extensive

and updated information about pros and cons of a prostate biopsy. Along with the video, the subject will be provided with a urology referral.

### 6.1.9 Testosterone and Hematocrit/Hemoglobin Management

All testosterone, Hct, and Hgb values will be blinded starting at Day 1.

If the serum total testosterone is > 750 ng/dL or Hct is > 54%, the IRT system will notify the site via an IRT notification to decrease dose by 1 actuation. The site will contact (e.g., by phone, via email, etc.) the subject and instruct the subject to reduce by one study drug actuation. After Week 26, the site will also ask the subject to return for a repeat blood draw 4 ± 1 weeks after dose reduction for both a serum total testosterone and Hct. Dose reductions and repeat blood draws may occur every 4 ± 1 weeks until the level decreases. If the serum total testosterone is > 750 ng/dL or Hct is > 54% even after dose titration to the lowest possible dose, the subject will be discontinued from study drug (Section 5.4.1). For Hgb value that is < 8.0 g/dL or > 18.9 g/dL, the unblinded medical monitor will review the lab value and notify the site for further action as appropriate.

If the subject does not return for a repeat blood draw, then the site should contact the subject (e.g., by phone, via email, etc.) at least twice to schedule a blood draw visit. If the subject is unwilling or unable to repeat the blood draw(s) as described above, then he may need to be discontinued from study drug.

Once a subject has down titrated a cumulative of 3 times for elevated Hct management, he will not have the opportunity to up titrate even if his testosterone results would dictate an up titration.

## 6.2 Product Complaint

### 6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product or to the medical device component(s).

For a product, this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

Any information available to help in the determination of causality by the device to the Product Complaints outlined directly above should be captured.

### 6.2.2 Reporting

Product Complaints concerning the study drug and/or device must be reported to AbbVie within 1 business day of the study site's knowledge of the event via the Product Complaint form in EDC. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to AbbVie (or an authorized representative) and documented in source as required by AbbVie. Product Complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition (bottle). In instances where a return is requested, every effort should be made by the Investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

## 7.0 Protocol Deviations

The Sponsor does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The Principal Investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is

identified, including those that may be due to the COVID-19 pandemic) after a subject has been enrolled, the Principal Investigator is responsible for notifying Independent Ethics Committee (IEC)/IRB regulatory authorities (as applicable), and his/her assigned CRO Clinical Monitor or the following AbbVie Clinical Monitor(s):

Primary Contact:

[redacted]
1 North Waukegan Road
R477, [redacted]
North Chicago, IL 60064

**OFFICE:** [redacted]
**MOBILE:**
**EMAIL:**

Alternate Contact:

[redacted]
1 North Waukegan Road
R477, [redacted]
North Chicago, IL 60064

**OFFICE:** [redacted]
**MOBILE:**
**EMAIL:**

Alternate Contact:

[redacted]
1 North Waukegan Road
R477, [redacted]
North Chicago, IL 60064

**OFFICE:** [redacted]
**MOBILE:**
**EMAIL:**

Alternate Contact:

[redacted]
1 North Waukegan Road
R477, [redacted]
North Chicago, IL 60064

**OFFICE:** [redacted]
**MOBILE:**
**EMAIL:**

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

**COVID-19 Pandemic-Related Protocol Deviation Documentation**

All COVID-19 related protocol deviations (e.g., missed visits, late visits, phone visits that should be in-person visits, temporary or permanent discontinuation of study drug, etc.)

must be documented in the subject's source documents and denoted that they were related to COVID-19.

# 8.0 Statistical Methods and Determination of Sample Size

## 8.1 Statistical and Analytical Plans

Unless noted otherwise, all analyses will be performed using SAS® version 9.3 (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

### 8.1.1 Analysis Sets

The following data sets will be used for the analyses of safety and efficacy endpoints for this study:

The Full Analysis Set (FAS) comprising all randomized subjects. Subjects will be categorized according to treatment assigned at randomization. The FAS will be mainly used for the summary of subjects' disposition and summary of subjects' demographics and Baseline characteristics for the study.

The Safety Set comprising all randomized subjects who receive at least one dose of study drug (TRT or placebo). Subjects will be categorized according to treatment received. Unless otherwise specified, the Safety Set will be used for the analysis of all safety endpoints of the study.

The Efficacy Analysis Sets (EAS) are pre-specified subgroups of the FAS comprising of eligible subjects from the main study who satisfy the criteria for sub-studies for sexual function, PDD, bone fracture, anemia and diabetes. The EAS will be used for the analyses of these sub-studies (Section 5.3.3 and Appendix O). For instance, the EAS for the analysis of sexual function sub-study will include subjects with Baseline DISF-SRII Section I: Sexual Desire domain score ≤ 20 (Section 5.3.3 and Appendix O).

### 8.1.2 Demographics, Other Baseline Characteristics, Subject Disposition and Concomitant Medication

Demographics and other Baseline data (including disease characteristics) will be summarized descriptively by treatment arm using the FAS.

Continuous data summaries, including at minimum the mean, standard deviation, median, minimum, and maximum, will be presented for age, height, weight, BMI, vital signs and laboratory assessments at Baseline.

Categorical data summaries will be presented as frequencies and percentages for race, ethnicity, age, pre-existing CV disease, prior use of testosterone (yes/no), and nicotine use (yes/no), alcohol use and physical exam data including vital signs.

For treatment comparisons and summaries, a Baseline value in general is defined as the last non-missing value obtained prior to or at the time of randomization unless specified otherwise in the analysis plan.

The number and percentage of subjects enrolled by investigator/institution will be provided. The number and percentage of subjects who are randomized, receive study drug, discontinue study drug, or discontinue the study will be summarized.

Prior and concomitant medications taken will be summarized.

### 8.1.3 Analysis of Treatment

Continuous summaries of subjects' total duration of treatment with study drug will be provided. Treatment duration will be computed as follows:

*Treatment duration = Date of last dose of study drug – date of first dose of study drug + 1.*

Total patient-years of exposure will be calculated by summing the duration of treatment for all subjects in the Safety Set and dividing this sum by 365.25 (= 1 year). In addition, the number and percentage of subjects exposed to study drug will be summarized for the

following categories of exposure duration: ≤ 1 month, > 1 to 2 months, > 2 to 3 months, > 3 to 6 months, > 6 months to 1 year, > 1 to 2 years, > 2 to 3 years, etc.

### 8.1.4 Analysis of Safety

#### 8.1.4.1 Primary Safety Endpoint

The primary endpoint of the study, time to MACE, is defined as time from randomization to the first occurrence of any component event of the composite MACE endpoint consisting of CV death, non-fatal MI and non-fatal stroke. Time to MACE for subjects who do not experience an event on study will be right-censored at the time of their last available follow-up observation.

A Cox proportional-hazards regression model will be used to estimate the hazard ratio of TRT to placebo and its two-sided 95% confidence interval (CI). The model will have the prior CV disease/risk as a covariate. The non-inferiority of TRT to placebo will be claimed if the upper limit of the 95% CI for hazard ratio rule out the margin of 1.5 following 256 events. Median time to event (TTE) and its 95% CI, as well as Kaplan-Meier (KM) estimates of the incidence function (cumulative event rates over time) will be calculated.

The primary analyses will include all MACE (i.e., time to the first occurrence of MACE for each subject with an event) reported in the study using the Safety Set and will be repeated using the FAS as supportive analyses.

**Principal Sensitivity Analyses for Primary Endpoint**

The principal sensitivity analyses will be performed based on 'on-exposure' period. In this analysis, MACE that occurs during the period from randomization to 365 days post last dose will be included. Events occurring after 365 days post last dose will be censored.

**Other Sensitivity/Supportive Analyses for Primary Endpoint**

Two other sensitivity analyses will be performed.

- Analysis only includes MACE that occurs during the period from randomization to 30-days-post last dose. Events occurring after 30-days-post last dose will be censored.
- For subjects with drug interruption(s) that was 3 months or longer, events occurring after 30-days-post the start date of the first interruption of 3 months or longer will be censored. For all other subjects, events occurring after 30-days-post last dose will be censored.

Additional sensitivity analyses may be performed where appropriate.

In addition, the restricted mean survival time (RMST) at 3-year based on the KM estimate will be obtained. When assumptions of constant hazards hold, the three measures of treatment difference, namely, hazard ratio (HR), risk difference, and RMST may be obtained as simple transformations of each other. Thus, assuming a background event rate of 1.5%, the decision threshold (non-inferiority margin) for absolute risk difference at 3 years and RMST at 3 years proportional to a HR of 1.5 under the constant hazards condition, respectively, is set to be 2.14% and –12 days as supportive analyses.

Component events of MACE will also be analyzed using similar methods. Categorical summaries of incidence of these events will also be provided.

#### 8.1.4.2 Secondary CV Safety Endpoints

Secondary CV safety endpoint is defined as time from randomization to first component event occurrence of the composite endpoint consisting of any of the following:

- Nonfatal MI
- Nonfatal stroke
- Death due to CV causes
- Coronary revascularization procedures/cardiac PCI and CABG

Time to secondary CV composite endpoint will be analyzed using similar methods as described in Section 8.1.4.1.

### 8.1.4.3 Secondary Prostate Safety Endpoints

The incidence of high grade prostate cancer (Gleason score of 4 + 3 or higher) will be summarized and will serve as a secondary safety endpoint and an event of special interest for prostate safety.

### 8.1.4.4 Other Safety Endpoints

**Tertiary Safety Endpoints**

The incidence of the following events will be summarized.

- All-cause mortality
- Heart failure events (hospitalization or urgent visit)
- Thromboembolic Events to include DVT/PE/venous thromboembolism (excluding superficial thrombophlebitis)
- Peripheral arterial revascularization

**Tertiary Prostate Safety Endpoints:**

- Prostate biopsy
- Any prostate cancer
- Acute urinary retention
- Starting pharmacologic treatment for lower urinary tract symptoms
- Invasive prostate surgical procedures (e.g., prostatectomy, transurethral prostate resection, brachytherapy or other prostate surgical procedure) for benign prostatic hyperplasia

**Adverse Events**

Treatment emergent AESI, AEs leading to study drug discontinuation and SAEs will be summarized by treatment group and overall in descending order of overall frequency by Medical Dictionary for Regulatory Activities (MedDRA) preferred term, as well as in a lexicographic order by system organ class (SOC) and MedDRA preferred term (PT).

Treatment emergent events are those that are reported from the time of study drug administration until 30 days following discontinuation of study drug. Treatment emergent AESI and SAEs will also be summarized according to their relationship to study drug and their maximum severity. In addition, treatment emergent AEs/SAEs that lead to study drug discontinuation will also be summarized.

**Clinical Laboratory Data**

Continuous summaries of mean changes from Baseline for items such as PSA, lipids, Hct and Hgb will be summarized and treatment group differences in change from Baseline to each post-Baseline Visit will be assessed.

**Vital Signs**

Continuous summaries of the mean change from Baseline to each visit in vital signs, including weight, will be provided. Vital sign variables include, but are not limited to, SBP, DBP, pulse rate, temperature, and weight.

### 8.1.5 Efficacy

The analysis of the efficacy endpoints will be detailed in the statistical analysis plan (SAP). For each of the five efficacy domains, the condition, the study population and the primary hypotheses have been pre-specified in Section 5.3.3 and Appendix O. The sample size for each efficacy endpoint (Table 8) is based on estimation of the defined relevant disease population and this study should be well powered to answer the efficacy endpoints and the sample size rationalized based on consideration of the hypothesized treatment effect and statistical power.

**Table 8. Sample Size for Efficacy Endpoints**

| Efficacy Domain | Condition/Study Population | Efficacy Endpoint | Estimated Sample Size | Power |
|---|---|---|---|---|
| Sexual function | Middle-aged and older hypogonadal men with low libido | Change from Baseline in overall sexual activity per PDQ Question 4 | 810 | 91% |
| Low grade, PDD (Dysthymia) | Middle-aged and older men with late-onset, low grade, PDD (dysthymia) | Proportion of men whose PDD remits during intervention per remission definition | 780 | 90% |
| Fracture | All men enrolled in the TRAVERSE Study | Proportion of men with adjudicated clinical bone fractures | 6000 | 90% |
| Diabetes | Middle-aged and older hypogonadal men with pre-diabetes at Baseline | Proportion of men, who had pre-diabetes at Baseline, and who progress to diabetes | 2430 | 90% |
| Anemia | Middle-aged and older hypogonadal men with unexplained anemia | Proportion of anemic men whose anemia is corrected during the intervention period | 576 | 90% |

Note: The sample sizes were based on 6,000 from the parent study and may be modified if sample size changes.

For serum testosterone, point-in-time testosterone levels will be evaluated to assess the percentage of men with serum testosterone levels in the normal range at different visits. Other exploratory analyses may be conducted as well, such as the relationship between changes in testosterone with changes in the selected efficacy endpoints during the study.

### 8.1.6 Interim Analyses

No interim analysis is planned for the study.

### 8.1.7 Type 1 Error Adjustment

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

## 8.2 Determination of Sample Size

This non-inferiority study plans to observe a total of 256 primary composite events (i.e., MACE) to rule out a HR of 1.5 at the 95% (2-sided) upper confidence limit (i.e., 1-sided alpha = 2.5%) with 90% power on the estimated annual placebo event rate of 1.5%, an accrual period of 3.5 years, and an annualized LTFU rate of 2%, a total of approximately 5,400 subjects (2,700 per treatment arm) are needed to observe the 256 required events for the primary analysis.

However, in order to achieve similar power for the principal sensitivity analysis (i.e., analysis to censor subjects after 365 days post last dose), approximately 6,000 subjects (in 3.5 year accrual period) will be needed assuming the treatment discontinuation rate is 20% in the first year, and 10% in the second year and thereafter.

Therefore, the study is planned to enroll approximately 6,000 subjects (3,000 per treatment arm), and the study will be stopped and analysis will be conducted after 256 MACE are observed for the principal sensitivity analysis. The study duration is projected to be 5.2 years under the alternative hypothesis (True HR = 1.0, i.e., no increased risk with TRT) and 4.4 years under the null hypothesis (True HR = 1.5).

### 8.2.1 Blinded Sample Size Re-Estimation (BSSR)

We note that certain design parameters may be different over the course of the study, most notably the assumed accrual rate, the annualized placebo event rate, and LTFU rate. Therefore, a periodic **blinded** review of the pooled study data will occur during the course of the study (e.g., after 4,500 subjects have been randomized or at approximately 2.5 years from the first subject enrolled).

The accrual rate and pooled event LTFU and treatment discontinuation rates will be evaluated against the original estimates used in the study design. The total number of subjects that will be enrolled for the study may be adjusted according to the observed pooled event rate, LTFU rate, as well as the accrual rate (the accrual period may need to be adjusted too) in order to obtain the target 256 events within the planned study duration

(i.e., approximately 5 years assuming no increased risk with TRT). The aforementioned adjustments and final sample size determinations will take this consideration into account.

**Detailed Methodology of the BSSR**

In general, for time-to-event analysis, sample size needed to achieve a certain number of events is a function of event rate (p), LTFU rate (d), accrual period (r), total study duration (t), and total required number of events (e). Thus, we can write the below formula for the sample size calculation, assuming constant hazard.

$$n = f(p, d, r, t, e)$$

In the study design, we assumed

$p = 1.5\%\ per\ year\ placebo\ arm, 1.5\%\ for\ TRT\ arm\ when\ HR = 1.0$

$d = 2\%\ per\ year$

$r = 4\ years$

$t = 5.2\ years\ when\ HR = 1.0$

$e = 256\ events$

Assume the BSSR is conducted at time $t_1$ from the first subject enrolled, and the following notations:

$n_1: number\ of\ subjects\ enrolled\ at\ t_1$

$e_1: number\ of\ events\ observed\ at\ t_1$

$p_1: pooled\ event\ rate\ observed\ at\ t_1$

$d_1: pooled\ LTFU\ rate\ at\ t_1$

For those subjects among $n_1$ who haven't had events yet, we can predict the additional number of events ($e_1'$) that will occur in the remaining of the study (i.e., in the interval from $t_1$ to $t$) based on observed event rate ($p_1$) and LTFU rate ($d_1$).

The additional sample size needed for the remaining of the study can be estimated as

$$n_2 = f(p_1, d_1, r_2, t_2, e_2)$$

Where $e_2 = 256 - e_1 - e_1'$; $t_2 = t - t_1$; and $r_2$ (accrual duration in the remaining of the study) can be adjusted if necessary.

Therefore, the total sample size will be $n = n_1 + n_2$.

### 8.3 Randomization Methods

Subject will be randomized via IRT system, using 1:1 randomization ratio and permuted block randomization, to receive either topical testosterone or placebo. Randomization will be stratified by pre-existing CV disease (Yes/No). Since the study is targeting at least 30% of randomized subjects enrolled in pre-existing CV disease cohort, and up to 70% of randomized subjects in CV Risk Factors cohort (i.e., no pre-existing CV disease); the proportions will be monitored and controlled via IRT system throughout the study. The ESC and Sponsor may decide to cap the CV risk factors cohort if that cohort is found to consistently exceed 70% of the total population enrolled or if the pooled primary event rate falls below projections.

## 9.0 Ethics

### 9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the current package insert, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the

ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The Investigator will be required to submit, maintain and archive study essential documents according to International Conference on Harmonization (ICH) GCP.

Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

## 9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

## 9.3 Subject Information and Consent

The Investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related Screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in

the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

Due to COVID-19 pandemic, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.

# 10.0 Source Documents and Case Report Form Completion

## 10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, CEC, and regulatory inspection(s), providing direct access to source data documents. The specific rules that apply to adjudicating events will be outlined within their respective charters (e.g., non-fatal MI adjudication criteria can be found in the CV events CEC charter).

## 10.2 Case Report Forms

The eCRF must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an EDC system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific eCRFs will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie or designee and will be maintained in the Trial Master File at AbbVie or the CRO.

The Investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The Investigator or an authorized member of the Investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The Principal Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the study through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the

Investigator at that time as a durable record of the site's eCRF data. It will be possible for the Investigator to make paper printouts from that media.

Patient reported data must be completed for each subject screened/enrolled in this study. Some of these data are being collected with an Electronic Patient Reported Outcome (ePRO) system called Trialmax, provided by the technology vendor Signant Health of Plymouth Meeting, PA, USA. The ePRO system is in compliance with Title 21 CFR Part 11. The documentation related to the system validation of the ePRO system is available through the vendor, Signant Health.

The subject will be entering the data on an electronic device; these data will be uploaded to a server. The data on the server will be considered source, and maintained and managed by Signant Health.

Internet access to the ePRO data will be provided by Signant Health for the duration of the study. This access will be available for the duration of the study to the site investigator, as well as delegated personnel. Such access will be removed from investigator sites following the receipt of the study archive. Data from the ePRO system will be archived on appropriate data media (CD-ROM, etc.) and provided to the Investigator at that time as a durable record of the site's ePRO data. It will be possible for the Investigator to make paper print-outs from that media.

The ePRO data will be collected by the following methods:

**Tablet Based**

The (instrument/scale) will be collected electronically via a tablet/laptop device into which the subject will directly enter the required pieces of information. The electronic device will be programmed to allow data entry for only the visits specified in the protocol and will not allow for subjects to complete more than one of the same assessments at any one visit. All data entered on the device will be immediately stored to the device itself and (manually/automatically) uploaded to a central server administrated by (ePRO Vendor). The Investigator and delegated staff will be able to access all uploaded subject

entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

**COVID-19 Pandemic-Related Acceptable Protocol Modifications**

Subjects may be brought in for an unscheduled visit to complete any questionnaires that were not done at the previous visits. These questionnaires will be recorded in the ePRO device under the previous visit name that was missed. They should be completed prior to the next scheduled on-site visit.

**Phone/Web Based**

The PDQ Question 4 (Appendix K) data for the sexual function sub-study (Appendix O) will be collected via the phone or through a web-based system.

## 11.0 Data Quality Assurance

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

## 12.0 Use of Information

Any research that may be done using optional exploratory research samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, the subject will not be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate data from optional exploratory research may be provided to Investigators and used in scientific publications or presented at medical conventions. Optional exploratory research information will be published or presented only in a way that does not identify any individual subject.

# 13.0 Completion of the Study

The Investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the Investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Investigator and AbbVie. The Investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The Investigator must retain any records related to the study according to local requirements. If the Investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

The EOS is defined as the date of the last subject last visit.

# 14.0 Investigator's Agreement

1. I have received and reviewed the product labeling for AndroGel 1.62%.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

| | |
|---|---|
| Protocol Title: | Testosterone Replacement therapy for Assessment of long-term Vascular Events and efficacy ResponSE in hypogonadal men (TRAVERSE) Study |
| Protocol Date: | 06 May 2021 |

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

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## Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by the Testosterone Replacement Therapy (TRT) Manufacturers Consortium are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie or their designee, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie or their designee and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.

8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

## Appendix B. List of Protocol Signatories

| Name | Title | Functional Area |
|---|---|---|
| [redacted] | [redacted] | Clinical |
| [redacted] | [redacted] | Clinical |
| [redacted] | [redacted] | Data and Statistical Sciences |
| [redacted] | [redacted] | Clinical Program Development |

## Appendix C. Study Activities

| **Months (Weeks)**<br>**Visit Windows**<br>**Week 2 ± 4 Days, Month 1, Month 3 ± 7 Days**<br>**Month 6 ± 14 Days**<br>**All Subsequent Visits ± 21 Days**<br>**Visits Timing Based on Time Elapsed from Baseline** | **SV1** | **SV2** | **SV3** | **D1 (Baseline)** | **W 2** | **M 1 W 4*** | **M 3 W 12** | **M 6 W 26** | **M 9 W 39 (phone)** | **M 12 W 52 (year 1)** | **M 15 W 65 (phone)** | **M 18 W 78** | **M 21 W 90 (phone)** | **M 24 W 104 (year 2)** | **M 27 W 116 (phone)** | **M 30 W 130** | **M 33 W 142 (phone)** | **M 36 W 156 (year 3)** | **M 39 W 168 (phone)** | **M 42 W 182** | **M 45 W 194 (phone)** | **M 48 W 208 (year 4)** | **M 51 W 220 (phone)** | **M 54 W 234** | **M 57 W 246 (phone)** | **M 60 W 260/FV (Year 5)** | **PD** | **Unscheduled** | **30-Day Call** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **INTERVIEWS & QUESTIONNAIRES** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | | X | X | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| CV Risk Assessment[a] | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Medical/Surgical History/Cancer History/CV Family History | | X | | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alcohol and Nicotine Use | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| AE Recording[b] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Prior/Concomitant Medication | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Site Endpoint Questionnaire Form | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Phone call | | | | | | | | | X | | X | | X | | X | | X | | X | | X | | X | | X | | | | X |
| Modified Rankin Scale[c] | | | | | | | | | | | | | | | | | | | | | | | | | | | | X | |

| **Months (Weeks)**<br>**Visit Windows**<br>**Week 2 ± 4 Days, Month 1, Month 3 ± 7 Days**<br>**Month 6 ± 14 Days**<br>**All Subsequent Visits ± 21 Days**<br>**Visits Timing Based on Time Elapsed from Baseline** | **SV1** | **SV2** | **SV3** | **D1 (Baseline)** | **W 2** | **M 1 W 4*** | **M 3 W 12** | **M 6 W 26** | **M 9 W 39 (phone)** | **M 12 W 52 (year 1)** | **M 15 W 65 (phone)** | **M 18 W 78** | **M 21 W 90 (phone)** | **M 24 W 104 (year 2)** | **M 27 W 116 (phone)** | **M 30 W 130** | **M 33 W 142 (phone)** | **M 36 W 156 (year 3)** | **M 39 W 168 (phone)** | **M 42 W 182** | **M 45 W 194 (phone)** | **M 48 W 208 (year 4)** | **M 51 W 220 (phone)** | **M 54 W 234** | **M 57 W 246 (phone)** | **M 60 W 260/FV (Year 5)** | **PD** | **Unscheduled** | **30-Dav Call** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PRO** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| I-PSS[d] | | X | | X | | | X | | | X | | | | | | | | X | | | | | | | | X | X | | |
| DISF – SRII Section I[e] | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HIS-Q | | | | X | | | | X | | X | | | | X | | | | | | | | | | | | X | X | | |
| PHQ-9 | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PGI-I Hypogonadism | | | | | | | | X | | | | | | X | | | | | | | | | | | | X | X | | |
| **EXAM** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Height & BMI, Weight | | X[f] | | X | | | X | | | X | | | | X | | | | X | | | | X | | | | X | X | | |
| Physical Examination | | X | | | | | X[g] | X[g] | | X[g] | | | | X[g] | | | | X[g] | | | | X[g] | | | | X[g] | X[g] | X[g] | |
| DRE | | X[h] | | | | | | | | X[i] | | | | | | | | X[i] | | | | | | | | X[i] | X[i] | X | |
| Vital Signs | | X | | X | X | X | X | X | | X | | | | X | | | | X | | | | X | | | | X | X | X | |
| 12-Lead ECG | | X | | | | | | | | | | | | | | | | | | | | | | | | X | X | X | |
| **CENTRAL LABS** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Testosterone[j] | X | X | X | | X[k] | X[k] | X[k] | X[k] | | X[k] | | X[k] | | X[k] | | | | X[k] | | | | X[k] | | | | X | X | X | |
| Free Testosterone | | X[l] | X[l] | | | | | | | X | | | | | | | | | | | | | | | | | | | |
| DHT, Estradiol | | | | X | | | | | | X | | | | | | | | X | | | | | | | | X | X | | |
| PSA | X[m] | | | | | | X | | | X[n] | | | | X | | | | X[n] | | | | X | | | | X[n] | X[n] | X | |

| **Months (Weeks)<br>Visit Windows<br>Week 2 ± 4 Days, Month 1, Month 3 ± 7 Days<br>Month 6 ± 14 Days<br>All Subsequent Visits ± 21 Days<br>Visits Timing Based on Time Elapsed from Baseline** | **SV1** | **SV2** | **SV3** | **D1 (Baseline)** | **W 2** | **M 1 W 4*** | **M 3 W 12** | **M 6 W 26** | **M 9 W 39 (phone)** | **M 12 W 52 (year 1)** | **M 15 W 65 (phone)** | **M 18 W 78** | **M 21 W 90 (phone)** | **M 24 W 104 (year 2)** | **M 27 W 116 (phone)** | **M 30 W 130** | **M 33 W 142 (phone)** | **M 36 W 156 (year 3)** | **M 39 W 168 (phone)** | **M 42 W 182** | **M 45 W 194 (phone)** | **M 48 W 208 (year 4)** | **M 51 W 220 (phone)** | **M 54 W 234** | **M 57 W 246 (phone)** | **M 60 W 260/FV (Year 5)** | **PD** | **Unscheduled** | **30-Dav Call** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hematology | | X | | X | | | | X | | X | | X | | X | | | | X | | | | X | | | | X | X | X | |
| HbA1c | | X | | | | | | | | X | | | | X | | | | X | | | | X | | | | X | X | X | |
| Fasting Glucose | | X | | X | | | | | | X | | | | X | | | | X | | | | X | | | | X | X | X | |
| Chemistry | | X | | | | | | | | X | | | | | | | | | | | | | | | | X | X | X | |
| Urinalysis | | X | | | | | | | | | | | | | | | | | | | | | | | | X | X | X | |
| hsCRP | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Serum Creatinine (eGFR assessment) (CKP-EPI equation) | | X | | | | | | | | | | | | | | | | | | | | | | | | X | X | | |
| **TREATMENT** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Randomization[o] | | | | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Dispense Study Drug | | | | X | X | X | X | X | | X | | X | | X | | X | | X | | X | | X | | X | | | | X | |
| Collect Study Drug | | | | | X | X | X | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | X | | |
| Study Drug Compliance Check & Discussion | | | | | X | X | X | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | X | | |

* Week 4/Month 1 Visit should be scheduled to occur about 10 days after the Week 2 visit to allow for testosterone to be resulted for titration. If the subject has not been on the Week 2 titrated dose prior to his scheduled Week 4/Month 1 Visit, the visit should be rescheduled.

a. CV risk should be initially assessed at SV1 and confirmed at SV2. It will be necessary to ask the subject about nicotine use to fully assess his CV risk (see Table 2).

b. Record AEs as described in Section 6.0.

c. The Modified Rankin Scale (Appendix P) will be administered to subject or subject representative at initial report of event and approximately 90 days following a reported stroke or TIA. This may be administered via telephone or in-person.

d. I-PSS greater than 19 is ONLY exclusionary at SV2.

e. Subjects with a DISF – SRII Section I ≤ 20 at SV2 (Appendix G) and consented to participation in the sexual function sub-study (Appendix O) need to complete the 7-day PDQ Question 4 (Appendix K) prior to Baseline (Day 1) Visit.

f. Height is only collected during the Screening Period to calculate BMI. BMI is only calculated during the Screening Period for the purpose of establishing a subject's eligibility (Section 5.2.2). Weight is collected at all visits as indicated.

g. All physical exams following Screening will be problem-focused/directed rather than full physical exams.

h. DREs performed outside the site within 6 months of SV1 are permitted as long as written documentation of the DRE result is provided.

i. DREs performed outside the site within ± 2 months of a protocol scheduled DRE are permitted as long as written documentation of the DRE result is provided.

j. Starting at SV2, serum testosterone samples should be drawn fasting. All screening serum testosterone samples will be collected between the hours of 5 AM and 11 AM.

k. Visits where study drug dose may be titrated.

l. Free testosterone will only be resulted from either SV2 or SV3 in subjects who are eligible for the study.

m. PSA will only be evaluated in subjects with testosterone levels < 300 ng/dL at SV1.

n. Blood draws assessing PSA should always be made prior to DRE, as prostate manipulation can falsely elevate PSA.

o. Only if all eligibility criteria are met.

## Appendix D. Event Reporting Example

| Event Type[a] | Category | Report in Rave® EDC System on AE/SAE Form | Report in Rave® EDC System on Endpoint (EP) Form | Submit Source for Adjudication in IBM Clinical | Exempt from Expedited IND/NDA Reporting[b] |
|---|---|---|---|---|---|
| **CV Events** | | | | | |
| Non-Fatal MI | Endpoint | YES | MI/Hospitalization for Unstable Angina and Potential MI EP Form | YES | YES |
| Non-Fatal Stroke | Endpoint | YES | Stroke and Potential Stroke EP Form | YES | YES |
| CV Death[b] | Endpoint | YES | Death EP Form | YES | YES |
| Non-CV Death | Endpoint | YES | Death EP Form | YES | NO |
| Coronary Revascularization Procedure/ PCI/CABG | Endpoint | YES[c] | Coronary Revascularization and Potential Coronary Revascularization EP Form | YES | YES |
| Heart Failure Event | Endpoint | YES | Heart Failure and Potential Heart Failure EP Form | YES | NO |
| Venous and Pulmonary Artery Thromboembolic Event | Endpoint | YES | Venous and Pulmonary Artery Thromboembolic and Potential Venous and Pulmonary Artery Thromboembolic EP Form | YES | NO |
| Peripheral Arterial Revascularization | Endpoint | YES[c] | Peripheral Arterial Revascularization and Potential Peripheral Arterial Revascularization EP Form | YES | NO |
| Hospitalization for Unstable Angina | AESI | YES | MI/Hospitalization for Unstable Angina and Potential MI EP Form | YES | NO |
| Non-fatal Arrhythmias Requiring Intervention | AESI | YES | N/A | NO | NO |
| Cardiovascular Disease causing Syncope | AESI | YES | N/A | NO | NO |

| Event Type[a] | Category | Report in Rave® EDC System on AE/SAE Form | Report in Rave® EDC System on Endpoint (EP) Form | Submit Source for Adjudication in IBM Clinical | Exempt from Expedited IND/NDA Reporting[b] |
|---|---|---|---|---|---|
| **CV Events (Continued)** | | | | | |
| TIA | AESI | YES | Stroke and Potential Stroke EP Form | YES | NO |
| **Prostate Events** | | | | | |
| Prostate Cancer | Endpoint | YES | Potential Prostate Cancer Site EP Form | YES | YES[d] |
| Acute Urine Retention | Endpoint | YES | Acute Urinary Retention/Invasive Prostate Procedure for BPH EP Form | YES | NO |
| Invasive Prostate Procedure (other than biopsy) | Endpoint | YES[c] | Acute Urinary Retention/Invasive Prostate Procedure for BPH EP Form | YES | NO |
| Lower Urinary Tract Symptoms or Prostate Enlargement Requiring Initiation of Pharmacological Therapy | Endpoint | YES | Acute Urinary Retention/Invasive Prostate Procedure for BPH EP Form | NO | NO |
| **Other Events** | | | | | |
| Bone Fracture | Endpoint | YES | Fracture EP Form | YES | YES |
| Diabetes (new or worsening) | Endpoint | YES | N/A | NO | NO |
| AE Leading to Study Drug Discontinuation (not listed above) | AE Leading to study drug discontinuation | YES | N/A | NO | NO |
| All Other SAEs (not listed above) | SAE | YES | N/A | NO | NO |

a. In order to assist the adjudication process, additional information on any potential events will be collected.

b. AbbVie Pharmacovigilance responsible for IND reporting. Definition of CV Death: an acute MI, sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to CV procedures, death due to CV hemorrhage, and death due to other CV causes.

c. Report the event that led to the procedure.

d. High grade prostate cancer (Gleason score of 4 + 3 or higher) are exempt from expedited IND reporting. All other incidents of prostate cancer should be reported.

## Appendix E. Site Endpoint Questionnaire Form Example

These forms represent content only. This form will be completed by the site.

**Visit Form (Subject to Be Queried at Each Phone and In-Person Visit)**

If any question is answered yes, the associated event should be entered on the AE CRF using the diagnosis, if known.

| Since the Last Visit… | Yes | No | Visit Not Done |
|---|---|---|---|
| Did Subject Die? | | | |
| Did Subject experience a Myocardial Infarction or Hospitalized for Unstable Angina? | | | |
| Did Subject have a Coronary Revascularization procedure attempted? | | | |
| Did Subject have a Peripheral Revascularization Procedure attempted? | | | |
| Did Subject have unplanned Urgent Visit or Hospitalization for Heart Failure? | | | |
| Did Subject experience a TIA or Stroke? | | | |
| Did Subject experience a Thromboembolic event (to include deep vein thrombosis, pulmonary embolus and other thromboembolic events)? Note: Does not include superficial thrombophlebitis | | | |
| Has the Subject had a PSA (Outside of the study)? | | | |
| Has the Subject had a DRE (Outside of the study)? | | | |
| Did the Subject have a Prostate Biopsy? | | | |
| Has the Subject been diagnosed with Prostate Cancer? | | | |
| Has the Subject been diagnosed with any other cancer besides Prostate Cancer? | | | |
| Did the Subject have an episode of inability to Pass Urine?* | | | |
| If so, was a catheter placed in the urinary bladder? | | | |
| Did this episode require a visit to the emergency room or a hospital? | | | |
| Was any prostate procedure done? | | | |
| Has Subject been started on new medication for Prostate Enlargement or Lower Urinary Tract symptoms? | | | |
| Has the Subject been diagnosed by a doctor or medical professional with a Fracture or Broken Bone? | | | |
| Has the Subject been diagnosed by a doctor or medical professional with Diabetes (new or worsening)? | | | |

* If one of these questions is answered 'YES,' the event should be reported on the endpoint form of Acute Urinary Retention/Invasive Prostate Procedure for BPH.

# Appendix F. International Prostate Symptom Score (I-PSS) Example

| INTERNATIONAL-PROSTATE SYMPTOM SCORE (I-PSS) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Not at all** | **Less Than 1 Time in 5** | **Less Than Half the Time** | **About Half the Time** | **More Than Half the Time** | **Almost Always** | |
| 1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating? | 0 | 1 | 2 | 3 | 4 | 5 | |
| 2. Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating? | 0 | 1 | 2 | 3 | 4 | 5 | |
| 3. Over the past month, how often have you found you stopped and started again several times when you urinated? | 0 | 1 | 2 | 3 | 4 | 5 | |
| 4. Over the past month, how often have you found it difficult to postpone urination? | 0 | 1 | 2 | 3 | 4 | 5 | |
| 5. Over the past month, how often have you had a weak urinary stream? | 0 | 1 | 2 | 3 | 4 | 5 | |
| 6. Over the past month, how often have you had to push or strain to begin urination? | 0 | 1 | 2 | 3 | 4 | 5 | |

| INTERNATIONAL-PROSTATE SYMPTOM SCORE (I-PSS) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Not at all** | **Less Than 1 Time in 5** | **Less Than Half the Time** | **About Half the Time** | **More Than Half the Time** | **Almost Always** | |
| | None | 1 time | 2 times | 3 times | 4 times | 5 or more times | |
| 7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning? | 0 | 1 | 2 | 3 | 4 | 5 | |
| Total I-PSS Score S = | | | | | | | |
| **QUALITY OF LIFE DUE TO URINARY SYMPTOMS** | | | | | | | |
| | **Delighted** | **Pleased** | **Mostly Satisfied** | **Mixed About Equally Satisfied and Dissatisfied** | **Mostly Dissatisfied** | **Unhappy** | **Terrible** |
| 1. If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that? | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Quality of life assessment index L = | | | | | | | |

## Appendix G. DeRogatis Interview for Sexual Function – Male (DISF – SR II)© Example

### DISF-SR II

**INSTRUCTIONS**

Included are a brief set of questions that ask about your sexual thoughts and feelings.

There are one or more scale definitions included with the questions.

The questions are quite brief, so please take your time in answering all the questions. **Please select the scale number for each question that best describes your personal experience.** If you have any questions, please ask the person who gave you the inventory for help or clarification.

---

**SEXUAL DESIRE**

**During the last 30 days,**

**1.1** How often did you have thoughts or fantasies about sexual, romantic, or erotic situations?
0 1 2 3 4 5 6 7

**1.2** How often did you feel sexual desire?
0 1 2 3 4 5 6 7

**1.3** How often did you want to be involved in sexual activities?
0 1 2 3 4 5 6 7

**1.4** With the partner of your choice, how often did you want to have sexual intercourse ?
0 1 2 3 4 5 6 7

**Questions 1.1 – 1.4**

7= 2 or more times a day
6= once a day
5= 4 to 6 times a week
4= 2 or 3 times a week
3= once a week
2= once or twice a month
1= less than once a month
0= Not at all

**Question 1.5**

**1.5** Usually, how strong was your sexual desire?
0 1 2 3 4 5

5= intense
4= very strong
3= strong
2= moderate
1= mild
0= absent

# Appendix H. Hypogonadism Impact of Symptoms Questionnaire (HIS – Q) Example

**Sexual Symptoms:**

These first questions ask about your sexual activities and experiences over the **past 14 days**. Sexual activities could include masturbation or sexual activities with a partner (including touching, oral stimulation, intercourse, or other activity).

| **Over the past 14 days…** | |
|---|---|
| 1. How many times did you engage in sexual activities? | _____ times |
| [*Programming note: If participants answer "0 times" to Question 1, Questions 2–5 and Questions 9–12 should be skipped*] | |
| 2. How many times did you initiate sexual activities? | _____ times |
| 3. How many times did you achieve an erection when you wanted to engage in sexual activities? | _____ times |
| 4. How many times did you maintain an erection for the entire time you were engaged in sexual activity? | _____ times |
| 5. How many times were you able to ejaculate (come)? | _____ times |

**Pop-up Instructions:**

For the remaining questions please select your response by touching the screen.

| **Over the past 14 days…** | | | | | |
|---|---|---|---|---|---|
| 6. Did you have sexual thoughts or fantasies? | Never | Rarely | Sometimes | Often | Always |
| 7. Did you feel sexual desire? | Never | Rarely | Sometimes | Often | Always |
| 8. How often did you experience morning erections? | Never | Rarely | Sometimes | Often | Always |
| 9. Did you have difficulty achieving erections when you wanted to? | Never | Rarely | Sometimes | Often | Always |
| 10. Did you have difficulty maintaining erections as long as you wanted to? | Never | Rarely | Sometimes | Often | Always |
| 11. Did you have difficulty ejaculating (coming)? | Never | Rarely | Sometimes | Often | Always |
| 12. Were sexual activities satisfying for you? | Never | Rarely | Sometimes | Often | Always |

These next questions ask about experiences that might be related to low testosterone over the **past 7 days**.

**Energy Symptoms:**

| Over the past 7 days… | | | | | |
|---|---|---|---|---|---|
| 13. How tired were you? | Not at all | A little | Moderately | Quite a bit | Extremely |
| 14. Did you have low energy? | Not at all | A little | Moderately | Quite a bit | Extremely |
| 15. How exhausted were you? | Not at all | A little | Moderately | Quite a bit | Extremely |

**Sleep Symptoms:**

| Over the past 7 days… | | | | | |
|---|---|---|---|---|---|
| 16. How much difficulty did you have getting enough sleep at night? | No difficulty | A little difficulty | Moderate difficulty | A great deal of difficulty | Extreme difficulty |
| 17. How often was your sleep restful? | Never | Rarely | Sometimes | Often | Always |
| 18. How often did you accidentally doze off during the day? | Never | Rarely | Sometimes | Often | Always |

**Cognition Symptoms:**

| Over the past 7 days… | | | | | |
|---|---|---|---|---|---|
| 19. How well were you able to focus your attention on tasks? | Not at all | A little | Moderately | Quite a bit | Extremely |
| 20. How forgetful were you? | Not at all | A little | Moderately | Quite a bit | Extremely |
| 21. Were you able to complete tasks efficiently? | Not at all | A little | Moderately | Quite a bit | Extremely |

**Mood Symptoms:**

| Over the past 7 days... | | | | | |
|---|---|---|---|---|---|
| 22. Did you feel sad? | Not at all | A little | Moderately | Quite a bit | Extremely |
| 23. Did you feel confident about yourself? | Not at all | A little | Moderately | Quite a bit | Extremely |
| 24. Did you feel irritable? | Not at all | A little | Moderately | Quite a bit | Extremely |
| 25. Did you feel impatient? | Not at all | A little | Moderately | Quite a bit | Extremely |
| 26. Did you feel motivated about things you needed to do? | Not at all | A little | Moderately | Quite a bit | Extremely |
| 27. Did you feel interested in doing leisure activities? | Not at all | A little | Moderately | Quite a bit | Extremely |
| 28. Did you feel that life was enjoyable? | Not at all | A little | Moderately | Quite a bit | Extremely |

## Appendix I. Patient Global Index of Improvement (PGI – I) Example

**All Subjects (PGI-Hypogonadism)**

Hypogonadism/overall global impression "Since the start of this study, I feel _____"
[very much better, much better, a little better, no change, a little worse, much worse, very much worse]

**Sexual Function Sub-Study Only (PGI-Libido)**

Libido – "Since the start of this study, my libido (sexual desire) is _____"
[very much improved; much improved; a little improved; unchanged; a little worse; much worse; very much worse]

**Persistent Depressive Disorder (PDD) Sub-Study Only (PGI-Mood)**

Depression – "Since the start of this study, my mood is _____"
[very much improved; much improved; a little improved; unchanged; a little worse; much worse; very much worse]

## Appendix J. International Index of Erectile Function (IIEF-5) Example

# The International Index of Erectile Function (IIEF-5) Questionnaire

**The International Index of Erectile Function (IIEF-5) Questionnaire**

| **Over the past 6 months:** | | | | | |
|---|---|---|---|---|---|
| 1. How do you rate your **confidence** that you could get and keep an erection? | Very low 1 | Low 2 | Moderate 3 | High 4 | Very high 5 |
| 2. When you had erections with sexual stimulation, **how often** were your erections hard enough for penetration? | Almost never/never 1 | A few times (much less than half the time) 2 | Sometimes (about half the time) 3 | Most times (much more than half the time) 4 | Almost always/always 5 |
| 3. During sexual intercourse, **how often** were you able to maintain your erection after you had penetrated (entered) your partner? | Almost never/never 1 | A few times (much less than half the time) 2 | Sometimes (about half the time) 3 | Most times (much more than half the time)4 | Almost always/always 5 |
| 4. During sexual intercourse, **how difficult** was it to maintain your erection to completion of intercourse? | Extremely difficult 1 | Very difficult 2 | Difficult 3 | Slightly difficult 4 | Not difficult 5 |
| 5. When you attempted sexual intercourse, **how often** was it satisfactory for you? | Almost never/never 1 | A few times (much less than half the time) 2 | Sometimes (about half the time) 3 | Most times (much more than half the time) 4 | Almost always/always 5 |

## Appendix K. Psychosexual Daily Questionnaire (PDQ) Question 4 Example

4. For all of the items below check yes if you have experienced (or are experiencing) today, otherwise check no.

| | Yes | No | | Yes | No | | Yes | No | |
|---|---|---|---|---|---|---|---|---|---|
| (a) | ☐ | ☐ | sexual daydreams | (e) | ☐ | ☐ | orgasm | (i) | ☐ | ☐ | masturbation |
| (b) | ☐ | ☐ | anticipation of sex | (f) | ☐ | ☐ | flirting (by others toward you) | (j) | ☐ | ☐ | night spontaneous erection |
| (c) | ☐ | ☐ | sexual interactions with partner | (g) | ☐ | ☐ | ejaculation | (k) | ☐ | ☐ | day spontaneous erection |
| (d) | ☐ | ☐ | flirting (by you) | (h) | ☐ | ☐ | intercourse | (l) | ☐ | ☐ | erection in response to sexual activity |

## Appendix L. Patient Health Questionnaire-9 (PHQ-9) Example

**PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)**

| Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✓" to indicate your answer)* | Not at all | Several days | More than half the days | Nearly every day |
|---|---|---|---|---|
| 1. Little interest or pleasure in doing things | 0 | 1 | 2 | 3 |
| 2. Feeling down, depressed, or hopeless | 0 | 1 | 2 | 3 |
| 3. Trouble falling or staying asleep, or sleeping too much | 0 | 1 | 2 | 3 |
| 4. Feeling tired or having little energy | 0 | 1 | 2 | 3 |
| 5. Poor appetite or overeating | 0 | 1 | 2 | 3 |
| 6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down | 0 | 1 | 2 | 3 |
| 7. Trouble concentrating on things, such as reading the newspaper or watching television | 0 | 1 | 2 | 3 |
| 8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual | 0 | 1 | 2 | 3 |
| 9. Thoughts that you would be better off dead or of hurting yourself in some way | 0 | 1 | 2 | 3 |

FOR OFFICE CODING 0 + _____ + _____ + _____
=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

| Not difficult at all | Somewhat difficult | Very difficult | Extremely difficult |
|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ |

## Appendix M. Geriatric Depression Scale (GDS-15) Example

***Instructions:*** Choose the best answer for how you felt over the past week. Note: when asking the patient to complete the form, provide the self-rated form (included on the following page).

| No. | Question | Answer | Score |
|---|---|---|---|
| 1. | Are you basically satisfied with your life? | YES / ***NO*** | |
| 2. | Have you dropped many of your activities and interests? | ***YES*** / NO | |
| 3. | Do you feel that your life is empty? | ***YES*** / NO | |
| 4. | Do you often get bored? | ***YES*** / NO | |
| 5. | Are you in good spirits most of the time? | YES / ***NO*** | |
| 6. | Are you afraid that something bad is going to happen to you? | ***YES*** / NO | |
| 7. | Do you feel happy most of the time? | YES / ***NO*** | |
| 8. | Do you often feel helpless? | ***YES*** / NO | |
| 9. | Do you prefer to stay at home, rather than going out and doing new things? | ***YES*** / NO | |
| 10. | Do you feel you have more problems with memory than most people? | ***YES*** / NO | |
| 11. | Do you think it is wonderful to be alive? | YES / ***NO*** | |
| 12. | Do you feel pretty worthless the way you are now? | ***YES*** / NO | |
| 13. | Do you feel full of energy? | YES / ***NO*** | |
| 14. | Do you feel that your situation is hopeless? | ***YES*** / NO | |
| 15. | Do you think that most people are better off than you are? | ***YES*** / NO | |
| | | TOTAL | |

(Sheikh & Yesavage, 1986)

***Scoring:***

Answers indicating depression are in bold and italicized; score one point for each one selected. A score of 0 to 5 is normal. A score greater than 5 suggests depression.

***Sources:***


- Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. *Clin Gerontol*. 1986 June;5(1/2):165-173.
- Yesavage JA. Geriatric Depression Scale. *Psychopharmacol Bull*. 1988;24(4):709-711.
- Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1982-83;17(1):37-49.

## Appendix N. Additional Persistent Depressive Disorder (PDD) Sub-Study Questions – Example

Baseline Questions administered only to men meeting PHQ-9 criteria for further PDD sub-study eligibility consideration outlined in Appendix O:

- Do you have any history of a major depressive episode? *Must be NO for enrollment in PDD sub-study*
- Have you had any mood disorder prior to age 40? *Must be NO for enrollment in PDD sub-study*
- Have you been treated for a mood disorder for longer than 6 months (e.g., antidepressant medication, psychotherapy)? *Must be NO for enrollment in PDD sub-study*

Q1: Given your best guess: over the past 2 years, have you been feeling sad or depressed more days than not even if you felt ok sometimes? *Must be YES for enrollment in PDD sub-study*

Q2: Again, given your best guess, over the past 2 years can you remember a period of time lasting 2 months or more when you were not feeling depressed much of the time? *Must be NO for enrollment in PDD sub-study*

Q3: Again, given your best guess, how old were you when you were last feeling okay, that is, not feeling depressed most days? *Must be ≥ 40 years of age for enrollment in PDD sub-study*

Q4: Have you ever been diagnosed by a doctor or mental health professional with a major depressive disorder or with bipolar disorder? *Must be NO for enrollment in PDD sub-study*

Q5: Have you ever felt so bad that you sought help from a mental health professional and had psychotherapy for more than 6 months? *Must be NO for enrollment in PDD sub-study*

Q6: Have you ever been prescribed an antidepressant for a mood problem, and took it for more than 6 months? *Must be NO for enrollment in PDD sub-study*

Q7: Have you ever felt so bad that you attempted suicide? *Must be NO for enrollment in PDD sub-study*

After Baseline, the following question will be asked of men enrolled in the PDD sub-study in addition to the questionnaires that subjects answer as part of the study

"Give your best guess: Over the past 6 months, have you been feeling sad or depressed more days than not even if you felt okay sometimes?"

## Appendix O. Sub-Studies and Sub-Population Analyses for Sexual Function, Persistent Depressive Disorder (PDD), Bone Fracture, Anemia and Diabetes

This section details the sub-studies, including the method of sub-population analyses, of five conditions in hypogonadal men that may benefit from TRT. As the impact of testosterone treatment on the incidence of fracture will be tested, all subjects participating in TRAVERSE will be asked if they experience a fracture throughout the study, and will be asked to supply source documents of the fracture for adjudication. Subjects with anemia or pre-diabetes at Baseline constitute sub-populations, which will be analyzed for resolution of anemia or slowing the progression to diabetes, respectively, based on analyses of laboratory data performed during the main study (e.g., Hgb, HbA1C, fasting glucose). The sexual function and PDD sub-studies of qualified participants will include additional ePRO questionnaires to be completed by the subjects during the study. To participate in one or more sub-studies, subjects must meet the eligibility criteria for that particular sub-study (detailed below). Subjects may participate in any or all of the sub-studies for which they are eligible. Subjects who are eligible for the main study but do not meet the eligibility criteria for a sub-study will only participate in the main study.

### 1. Sexual Function Sub-Study

The sexual function sub-study will require additional ePRO questionnaires to be completed by the subjects who meet the eligibility criteria as shown below. If subjects complete less than 4 of 7 days (e.g., Day –7 to Day –1) for the Baseline (Day 1) PDQ assessment, then they will be discontinued from the Sexual Function Sub-Study.

#### Background

Sexual symptoms are the most common reason that motivates men to seek testosterone treatment. Yet, there are limited data on the efficacy of TRT in improving sexual function in men with age-related decline in circulating testosterone. A recent randomized study reported greater improvements in sex drive and energy with 12 weeks of TRT versus placebo in hypogonadal men ages 19 to 80 years.[32] The sexual function study of the

T-Trials reported improvements in sexual desire, erectile function and sexual activity in men 65 years or older with low libido and low serum testosterone.[32,57] Since the T-Trials did not study men less than 65 years of age, it is important to determine the benefits on sexual function of TRT in middle-aged men, and whether the benefits in older men observed previously are durable over time and whether these benefits can be seen in men with CV disease and CV risk who are at higher risk of having sexual symptoms. Accordingly, the sexual function sub-study will determine the efficacy of TRT in improving sexual activity and function in middle-aged and older hypogonadal men with low libido who have increased CV risk and will determine the durability of treatment effect beyond the first year of intervention.

**Objective**

This sub-study will examine whether TRT (relative to placebo) improves overall sexual activity, sexual desire, and erectile function (change from Baseline in ePRO).

**Eligibility**

***Inclusion Criteria***

- Low libido ascertained by DeRogatis Interview for Sexual Function-Male (DISF-SRII)[47] Section I score ≤ 20 at SV2
- Willingness to participate in the sexual function sub-study

**Efficacy Variables**

Sexual function sub-study will include subjects who have low libido, as indicated by DISF-SRII Section I score ≤ 20 at Baseline (collected SV2).

Endpoints all pertain to middle-aged and older men with low libido, and include:

- Determine whether TRT for 1 year improves overall sexual activity, using Question 4 of the PDQ, more than placebo (Main analysis variable).
- Determine whether TRT for 1 year improves sexual desire, using the libido domain of HIS-Q instrument, more than placebo.

- Determine whether TRT for 1 year improves erectile function, using the erectile function domain of the IIEF, more than placebo.
- Determine whether improvements in sexual activity, sexual desire, and erectile function over 1 year are maintained after 2 years of TRT versus placebo.
- Exploratory endpoint: Compare the effect of TRT versus placebo therapy on patient global impression of change in sexual function using a patient global impression of change (PGI-I Libido) question.

### Additional Sexual Function Sub-Study Activities

| **Months (Weeks) Visit Windows Day 1 ± 4 Days, Month 6 ± 14 Days All Subsequent Visits ± 21 Days Visits Timing Based on Time Elapsed from Baseline** | **7 Consecutive Days Prior to Day 1** | **D1** | **M 6 W 26** | **M 12 W 52** | **M 24 W 104** | **M 60 W 260/FV (Year 5)** | **PD** |
|---|---|---|---|---|---|---|---|
| IIEF-5 | | X | | X | X | | |
| PDQ Question 4[a] | X | | X | X | X | | |
| PGI-I Libido | | | | X | X | X | X |

a. Subjects meeting the inclusion criteria for sexual function sub-study following SV2 (above) need to complete the 7-day PDQ Question 4 (Appendix K) prior to Day 1 Visit (Baseline).

## 2. Persistent Depressive Disorder (PDD) Sub-Study

The PDD sub-study will require additional ePRO questionnaires to be completed by the subjects who meet the eligibility criteria as shown below.

### Background

Epidemiologic evidence shows that,[58,59] mid-life, low grade depression (dysthymia or PDD) is associated with low testosterone in men. Studies investigating the impact of testosterone therapy have not observed improvement in men with major depressive disorder (MDD),[60] but other studies have observed that testosterone therapy can improve

depressive (dysthymia or PDD) symptoms in men with low-grade, mid-life-onset PDD.[61-63]

This sub-study will examine whether TRT (relative to placebo) improves depressive symptoms in men with low-grade, mid-life-onset PDD.

**Eligibility**

***Inclusion Criteria***

- Willingness to participate in the PDD sub-study

Inclusion criteria for the PDD ("depression") sub-study include men who meet any of the below PHQ-9 criteria from SV2:

- Total PHQ-9 score > 4
- PHQ-9 Item 2 score of 1 or 2
- PHQ-9 Item 10 score of > 0

Additionally, men must not meet any of the below PHQ-9 criteria from SV2:

- Total PHQ-9 score > 15
- PHQ-9 Items 1 or 2 score of 3
- PHQ-9 Item 9 score of > 0

If subjects do not complete (i.e., partially or not at all) the PHQ-9 at Screening and/or GDS questionnaires with related depressive questions at Baseline, then they will be discontinued from the PDD Sub-study.

ePRO tablet programming will identify men that meet the above preliminary PHQ-9 depression sub-study eligibility criteria from SV2. At the Baseline Visit, these men will then be asked additional eligibility questions (Appendix N) to assess their eligibility for the PDD sub-study via the PRO tablet based on questions (Appendix N) adapted from the

diagnosis of PDD as described in Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[64] criteria for PDD with low-grade symptoms.

Finally, men who are still eligible via the above criteria will be asked to take the GDS-15 questionnaire. Men with GDS-15 (Appendix M) scores between 5 – 9 will then be entered into the PDD sub-study.

If subjects respond to any of the above questions in a way that makes them ineligible for the PDD sub-study, the tablet will skip the remainder of the questions related to PDD sub-study eligibility.

***Exclusion Criteria***

- Lifetime history of any major depressive episode
- Onset of any mood disorder prior to age 40 years
- History of treatment for a mood disorder longer than 6 months (e.g., antidepressant medication, psychotherapy)
- History of a suicide attempt

**Efficacy Variables**

The remission of low-grade, late-onset PDD will be defined by both of the following criteria: (Main analysis variable)

a. GDS-15 < 5

   AND

b. Response to the question: "Over the past **6 months**, have you been feeling sad or depressed more days than not even if you felt okay sometimes?" = no

The primary analyses will compare the proportion of men with low grade PDD at Baseline who go into remission in the placebo and testosterone arms.

- Other analyses will include:

- Changes in depression symptom scores using PHQ-9, GDS-15 and HIS-Q (Mood domain)
- Proportion of men achieving remission at 12 months who remain in remission at 24 months

**Additional PDD Sub-Study Activities**

| **Months (Weeks)**<br>**Visit Windows**<br>**Day 1 ± 4 Days**<br>**Month 6 ± 14 Days**<br>**All Subsequent Visits ± 21 Days**<br>**Visits Timing Based on Time Elapsed from Baseline** | **D1** | **M 6 W26** | **M 12 W 52** | **M 18 W 78** | **M 24 W 104** | **M 60 W 260/FV (Year 5)** | **PD** |
|---|---|---|---|---|---|---|---|
| PHQ-9 | | X | X | X | X | | |
| Additional Persistent Depressive Disorder (PDD) Questions | X | X | X | | X | | |
| GDS | X | X | X | | X | | |
| PGI-I Mood | | | X | | X | X | X |

**Discontinuation from Study**

Subjects at risk of suicide as indicated by a response greater than 0 on Question 9 of any post Baseline PHQ-9 and/or determined by the Investigator to be at risk of suicide should be discontinued from participation in the study and referred for appropriate follow-up care (Section 5.4.1).

**3. Bone Fracture Sub-Study (Analysis Only)**

Subjects will be asked whether or not they experienced a fracture since their last visit at every in-person and telephone study visit. The subjects who report fractures during the study will be asked to provide all documentation of the fractures so that the events can be adjudicated. The adjudicated events will be analyzed to compare the incidences of fracture in subjects on TRT versus placebo.

**Background**

Approximately 30% of fractures occur in men, and mortality after a fracture is higher in men than in women.[65-67] Although, age alone is likely an important cause of fractures in men, evidence suggests that hypogonadism associated with age is also an important cause.[68] Testosterone treatment improves bone structure and strength of severely hypogonadal men,[69-73] but testosterone treatment also improves bone structure and strength in older men with low testosterone due to aging alone.[73] In the T-Trial bone sub-study, testosterone treatment for 1 year improved volumetric BMD of whole bone in the spine by 4.2% more than placebo ($P < 0.001$) and in the hip by 1.3% more than placebo ($P < 0.001$). This treatment also improved whole bone strength, as estimated by finite element analysis, by 7.1% ($P < 0.001$) in the spine and 1.8% ($P < 0.001$) in the hip more than placebo.[73] In the TRAVERSE study, we will assess the impact of testosterone on the incidence of clinical fractures in men with CV disease and men with CV risk factors.

**Objective**

This sub-study will examine the effect of TRT (relative to placebo) on incidence rate of adjudicated clinical bone fractures.

**Efficacy Variable**

Determine if the incidence of clinical fracture, confirmed by adjudication, is reduced in subjects treated with TRT versus placebo. Secondary fracture outcomes will be non-spine clinical fractures and hip fractures.

**4. <u>Anemia Sub-Study</u> (Analysis Only)**

Subjects must meet the eligibility criteria as described below in order to qualify for this sub-study.

**Background**

The prevalence of anemia rises with advancing age, affecting approximately 10 – 12% of men > 65 years old and 20 – 30% in men > 85 years old, and is often associated with

diminished physical function.[37,74-83] Unexplained anemia of aging is characterized by a decrease in circulating hemoglobin (usually between 10.0 to 12.7 g/dL) with normocytic red cell indices. The pathophysiology is multifactorial, with low testosterone levels being implicated[81,84] along with other factors. Testosterone is known to increase Hgb and Hct through various mechanisms, including stimulation of erythropoietin secretion, increased sensitivity to erythropoietin, and increased iron availability through suppression of hepcidin. Therefore, this large prospective study aims to determine the efficacy of testosterone therapy in correcting anemia in hypogonadal men with Hgb values below 12.7 g/dL at Baseline.

**Objective**

This sub-study will examine the efficacy of TRT (relative to placebo) in correcting anemia in middle-aged and older hypogonadal men.

**Eligibility**

***Inclusion Criterion***

- Hgb level ≥ 10 g/dL and < 12.7 g/dL

***Exclusion Criterion***

- The use of any other erythropoietic stimulating agents, such as erythropoietin

**Efficacy Variables**

Randomized subjects with a Hgb of < 12.7 g/dL at Baseline will be evaluated for outcomes of interest, including:

- The proportion of men who have anemia at Baseline but who are no longer anemic (Main analysis variable)
- The proportion of men with anemia at Baseline whose Hgb increases by more than 1 g/dL

- Exploration of possible relationship between improvement in anemia and change in energy domain score and the cognition domain score of HIS-Q [complete blood count (CBC) and HIS-Q are obtained throughout the parent study]

## 5. Diabetes Sub-Study (Analysis Only)

Subjects must meet the eligibility criteria as described below in order to qualify for this sub-study.

### Background

TRT may retard progression from pre-diabetes to diabetes with studies showing that testosterone supplementation in middle-aged men with truncal obesity and low-normal testosterone levels is associated with a reduction in visceral fat volume, serum glucose concentration, and an improvement in insulin sensitivity.[42-45, 85-95] Use of long acting gonadotropin-releasing hormone (GnRH) agonists which inhibit testosterone to castrate levels increase fat mass in young men[94] and increase the risk of diabetes and CV disease when given to men for prostate cancer.[96] While the effects of testosterone on insulin sensitivity are mostly clear,[97] the effects of testosterone on improving HbA1c in diabetes are inconsistant.[36] The TRAVERSE study provides a clear opportunity to determine the effects of TRT on progression from pre-diabetes to diabetes given its extended duration and large sample size.

### Objective

This sub-study will examine whether TRT (relative to placebo) is associated with a lower rate of progression to Type 2 diabetes mellitus in middle-aged and older hypogonadal men with pre-diabetes.

**Eligibility**

***Inclusion Criterion***

- A diagnosis of pre-diabetes, based on HbA1C level between 5.7 and 6.4%, inclusive or two fasting glucose levels between 100 and 125 g/dL, inclusive

***Exclusion Criterion***

- A diagnosis of diabetes or use of diabetes medication at Baseline
- HbA1c ≥ 6.5% at Screening
- Fasting glucose > 125 g/dL at Screening or Baseline Visit

**Efficacy Variable**

The proportion of enrolled subjects in each arm with pre-diabetes at Baseline who progress to diabetes, defined as HbA1c ≥ 6.5%, initiation of diabetes medication, or two fasting glucose levels > 125 mg/dL.

## Appendix P. Modified Rankin Scale

| Scale | Disability |
|---|---|
| 0 | No symptoms at all |
| 1 | No significant disability despite symptoms; able to carry out all usual duties and activities |
| 2 | Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance |
| 3 | Moderate disability; requiring some help, but able to walk without assistance |
| 4 | Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance |
| 5 | Severe disability; bedridden, incontinent and requiring constant nursing care and attention |
| 6 | Dead |

## Appendix Q. Coronary Artery Disease Definition

This appendix is to clarify for study investigators and study coordinators the entry criterion of coronary disease through evidence of percentage stenosis by angiogram from Table 1 (Pre-Existing CV Disease).

Coronary artery-specific considerations:

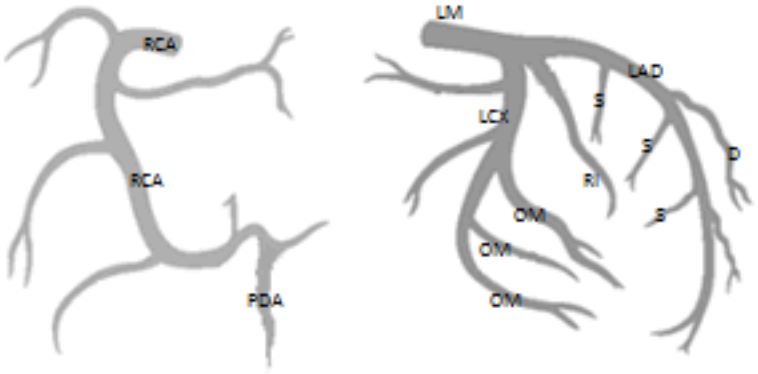
- The typical coronary anatomy consists of the left main artery (LM) arising from the left coronary sinus and the right coronary artery (RCA) arising separately from the right coronary sinus. The left main gives rise to the left anterior descending (LAD) and left circumflex (LCX) arteries. Because the LM supplies the LCX and LAD, a stenosis (blockage) in the LM will count as the two artery distributions required for the criteria.
- The LAD and LCX also have branches. The branches from the LCX are termed obtuse marginal (OM) or lateral (including "posterolateral") branches and the ramus intermedius. The branches from the LAD are termed diagonal and septal branches. Obstruction of one of these branch vessels will be considered as qualifying as a stenosis in that coronary distribution.
- "Right dominance" – The RCA, courses around the right side of the heart and usually gives off a posterior descending artery (PDA) that runs down the back of the heart between the ventricles. In most patients, the PDA arises from the RCA (termed "right dominance").
- "Left dominance" – In approximately 10% of patients, the PDA arises from the LCX artery (termed "left dominance"). *(Thus, stenosis of the proximal LCX in a left-dominant system affects two arterial distributions)*. In a left dominant circulation, the RCA is small and supplies blood to the right ventricle only, and is not considered a major coronary distribution.

In order to meet this eligibility criterion, "Evidence of coronary disease (at least a 50% lesion in two of the major coronary artery distributions including their branches) as documented by angiogram" one of the following must be present:

- stenosis in the LM coronary artery

- in a right dominant system (see above), stenoses in any two of the three major arteries (LCX, LAD, or RCA) including branches of those arteries
- in a left dominant system (see above): any one of the following:
  - stenoses in the LAD (or branches) AND LCX (or branches)
  - stenosis in the proximal LCX
  - stenoses in the ramus intermedius or an OM branch AND in the distal LCX or PDA

**Figure 3. Right-Dominant and Left-Dominant Circulations**




**Right Dominant Circulation**


**Left Dominant Circulation**

**Key**

D: Diagonal
LAD: Left Anterior Descending
LCX: Left Circumflex Artery
LM: Left Main
OM: Obtuse Marginal
PDA: Posterior Descending Artery
RCA: Right Coronary Artery
RI: Ramus Intermedius
S: Septal