PASS Information

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2. List of Abbreviations

Term	Definition
DVT	deep venous thrombosis
eTT	exogenous testosterone treatment
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
ICD-9 CM	International Classification of Diseases, Ninth Revision, Clinical Modification
CI	Confidence Interval
IR	incidence rate
KS	Klinefelter's syndrome
Marketscan	Truven Health MarketScan® Research Databases
OR	odds ratio
PE	pulmonary embolism
PPV	positive predictive value
THAM	Truven Health Analytics MarketScan
TT	total testosterone level
US	United States
VTE	venous thrombotic event

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4. Abstract

Title: The Risk of Venous Thrombotic Events among Males Treated with Testosterone Replacement Therapy

Version: 1.0. **Date:** 26 September 2013

Rationale and background: Venous thromboembolism or venous thrombotic event (VTE) often manifests as deep vein thrombosis (DVT) or pulmonary embolism (PE). A number of studies have focused on the epidemiology of VTE among the general population. A recent literature review indicates that major risk factors for thrombosis, other than age, are exogenous factors such as surgery, hospitalization, immobility, trauma, pregnancy and the puerperium and estrogenic hormone use, and endogenous factors such as cancer, obesity, and inherited and acquired disorders of hyper coagulation. No studies were identified in the literature assessing thromboembolic events among the untreated hypogonadal patients. The proposed study is to further investigate whether there is an increased risk of VTE among patients treated with testosterone replacement therapy in comparison to untreated hypogonadal patients.

Research question and objectives: The primary objective of this study is to estimate the incidence rates (IRs), and hazard ratio (HR) of VTE among a hypogonadal cohort initiating any testosterone products relative to a comparison group without testosterone replacement therapy. The secondary objective is to further estimate the crude and adjusted odds ratio (OR) for the association between exogenous testosterone treatment (eTT) and VTE in a nested case-control study setting for validation purpose to reinsure the rigorousness of the study design and the robustness of the study findings from. The 2 designs should, in theory, yield similar results. The specific objectives to be assessed are as follows:

- **Primary Objective:** To evaluate the VTE risk using cohort study design by estimating the **incidence rates (IRs), and hazard ratio (HR)** of VTE among patients treated with testosterone replacement therapy (overall and by different routes of administration) relative to a propensity score matched untreated comparison group
- **Secondary Objective:** To evaluate the VTE risk using a nested case-control study within original cohort by estimating the **crude and adjusted odds ratio (OR)** of VTE for patients exposed to testosterone products (overall and by different routes of administration) compared to untreated patients

Study design: A retrospective cohort study is proposed as a primary study design, with a nested case-control study as a secondary study design. **The retrospective cohort observational study** will use medical claims, pharmacy data and enrollment information from electronic claims records in the United States (US) to assess the crude and adjusted incidence rate of VTE among patients newly treated with any testosterone products relative to patients without testosterone treatment matched on baseline characteristics and calendar time. **A nested case-control study** will be performed within the original hypogonadal cohort. For each VTE case, 4 controls without VTE will be selected from the original hypogonadal cohort matched to the case on index date and age (±1 year). This study design has advantages for studying shortened exposures or switched drug exposures. No chart abstraction is provided in the present study, but the claims of each VTE case will be adjudicated by clinicians with experience. Patients' characteristics and

VTE risk factors including relevant medical and drug exposure information will be defined and compared between VTE cases and controls based upon the data availability.

Population: The source population will consist of hypogonadal patients in the database with at least **12 months (365 days)** of continuous enrollment in the health plan prior to the index date. The index date is the first prescription date for patients treated with testosterone. The medical claims data will contain 12 months preceding cohort entry to characterize baseline variables for study subjects. Propensity score matching will be used to ensure comparability between treated and untreated cohorts based on their baseline characteristics.

Inclusion criteria: Subjects are eligible for inclusion if they meet the following criteria:

- Males aged 18 years or older
- Males with a hypogonadal condition
    - Treated hypogonadal patients will be identified within the database who received at least 1 prescription for testosterone product. They are new users of testosterone treatment therapy who do not have a usage during the baseline.
    - Untreated hypogonadal patients who had the diagnostic codes for hypogonadal conditions during a clinic visit but did not receive any testosterone prescriptions at this time will be identified as an initial comparison cohort.
- Continuous enrollment in the health plan (medical and prescription) for a minimum of 12 months prior to index date. Continuous enrollment will be defined as no enrollment gap exceeding 31 consecutive days at any given time in the course of the study.

Exclusion criteria: Subjects will be excluded from the study if they meet the following criteria:

- Female gender or dual gender
- Subjects with baseline VTE events

Variables:

The exposure variable is any testosterone replacement therapy, categorized by prespecified routes of administration: transdermal gel, transdermal patch, injection, and other testosterone use.

The study outcome is incident VTE, which refers to DVT and PE.

Baseline characteristic variables will include demographics, resource utilization, comorbidities, VTE risk factors, and any medication use during baseline period.

VTE Risk Factors:

- Non-modifiable risk factors: age, genetic/congenital factors (primary hypercoagulable state: factor V Leiden mutation, antithrombin III deficiency, etc.), and inherited hypercoagulable syndrome

- Modifiable factors/acquired risk factors: cancer diagnosis and treatment, metabolic disorder, chronic renal disease, cardiovascular disease, varicose vein, rheumatoid arthritis, sepsis, and inflammatory bowel disease
- Temporary risk factors: fracture of pelvis, hip or lower limb, major surgery, trauma, and hospitalization

Data sources: The present study will utilize a US-based electronic claim database: Truven Health MarketScan ® Database.

Study size: A feasibility assessment to determine the sample size and study power has been conducted. Assuming incidence rate of VTE in reference group (untreated) is 1.5% and the difference between treated group of 1.0%, 1:1 ratio for the 2 treatment arms (treated: untreated), and a two-sided α of 0.05, there will be around 80% power using 3229 patients to detect statistical significant in the incidence rate of VTE.

Data analysis: The primary analysis of this protocol is to compare the percentage of patients who developed incident VTE after index date in treated patients who received at least 1 prescription of any testosterone products versus untreated patients who have not received any testosterone prescription. Propensity score matching method will be applied to select untreated cohort and match to treated cohort. Cox regression model will be used to estimate the incidence rate and hazard ratio. For the secondary (nested case-control) analysis, the conditional logistic regression is planned for univariate and multivariate analyses. The association between testosterone exposure patterns (current and past exposure of testosterone) will be reported as crude and adjusted OR representing the testosterone exposures relative to non-testosterone users.

5. Amendments and Updates

Not applicable.

6. Milestones

Milestone	Planned Date
Start of data collection	07 October 2013
End of data collection	Q2 2014
<Registration in the EU PASS register> [EU PASS Only]	Estimated Q2 2014
Final report of study results	Q3 2014

7. Rationale and Background

7.1. Background for Venous Thromboembolism

Venous thromboembolism or VTE often manifests as DVT or PE. DVT is defined as a blood clot in 1 or more of the deep veins of the legs, arms, pelvis, neck, axilla, or chest. PE is an obstruction of blood vessel in the lungs, usually due to a blood clot which blocks a coronary artery. A number of studies have focused on the epidemiology of VTE. The annual incidence rate is about 1 per 1000 adults, and rises exponentially from <5 per 100,000 for patients <15 years of age to 500 per 100,000 (0.5%) persons at age of 80 years (White 2003). The incidence rate increases sharply at approximately 45 years of age and is slightly higher in men than women in older age groups (Cushman 2007). About two-thirds of VTE episodes manifest as DVT and one-third as PE with or without DVT. The major outcomes of VTE are death, recurrent post-thrombotic syndrome, and major bleeding due to anticoagulation. Death occurs within 1 month of an episode in about 6% of those with DVT and 10% of those with PE (Cushman et al. 2004; Cushman 2007). The mortality rate of PE has been estimated to be as high as 30%. Mortality rates are low among patients with idiopathic VTE and highest among those whose thrombosis occurs in the setting of cancer (Heit et al. 1999).

VTE Risk Factors

VTE used to be viewed primarily as a complication from either major surgery or late-stage terminal illness (. A recent literature review indicates major risk factors for thrombosis, other than age, include exogenous factors such as surgery, hospitalization, immobility, trauma, pregnancy and the puerperium and estrogenic hormone use, and endogenous factors such as cancer, obesity, and inherited and acquired disorders of hypercoagulation. The risk factors are summarized and presented in Section 9.3.4, which is supported by current knowledge and epidemiologic studies (Cushman 2007; Goldhaber 2010; Stein and Matta 2010).

To date, no study has reported that low testosterone level or hypogonadism is associated with the risk of VTE. It is well known that hormone replacement therapy in menopausal or postmenopausal women is associated with an increased risk of VTE (Canonico et al. 2007), and testosterone is converted by aromatase to estradiol; however, both endogenous testosterone level and estrogens were not related to VTE risk in a prospective, population-based Thromso study (Svartberg et al. 2009). Further the study suggested that low endogenous testosterone is not one of the risk factors of VTE. Likewise, higher levels of testosterone were not related to VTE risk. For example, anabolic steroid abuse has been linked to acute vascular events but not acute thrombosis risk among athletes (Svartberg et al. 2009). Therefore, there is no direct evidence that physiological testosterone levels or treatment doses are thrombogenic.

7.2. Background for Hypogonadism and Treatment Options

Hypogonadism in men, characterized by a reduced concentration of serum testosterone, causes a constellation of signs and symptoms that may include decreased libido, erectile dysfunction, decreased volume of ejaculate, loss of body and facial hair, weakness, decreased bone density, decreased lean body mass, increased body fat, fatigue, and anemia

(Petak et al. 2002). Studies have showed an increased risk of certain morbidity conditions among aging hypogonadal men, including a higher prevalence of depression (Delhez et al. 2003), osteoporosis (Szulc et al. 2003), cardiovascular morbidity, and mortality (Corona et al. 2011). Although low testosterone level has been associated with CVD risk factors and increased risk for CVD in men, and VTE and arterial thromboembolism shared some of these risk factors, no study has reported a positive association between testosterone level and VTE risk. Furthermore, the Tromso study, a prospective population-based study in men, concluded that endogenous testosterone hormone levels were not associated with the risk of VTE (Svartberg et al. 2009). **Treatment of hypogonadism** with testosterone supplementation in the United States has increased substantially over the past several years, with a 5-fold increase in prescription sales of testosterone products since 1993 (Muller et al. 2012). Different forms of testosterone are available for administration, including injectable, transdermal, buccal, and oral testosterone formulations for clinical use.

No studies were identified in the literature assessing if there is increased thromboembolic risk among the hypogonadal-treated patients relative to untreated patients. Two studies were identified that reported the incidence rate of DVT among men treated with exogenous testosterone. One study reported DVT occurring in a patient with normogonadotropin hypogonadism possibly related to testosterone replacement (Androgel) (1/163 or 0.6%) and another reported DVT in 1 hypogonadal patient also possibly related to long-acting testosterone undecanoate injection (1/130 or 0.8%) (Wang et al. 2004; Morgentaler et al. 2008). Another exploratory study published recently suggested a thrombotic interaction between exogenous testosterone and thrombophilia-hypofibrinolysis (Glueck et al. 2013). The proposed study is to further investigate whether there is an increased risk of VTE among hypogonadal patients with testosterone replacement therapy relative to untreated patients.

8. Research Question and Objectives

To date, there are no robust data to support the association between eTT and VTE despite the potential link of testosterone use and increased hematocrit/hemoglobin level. The overall goal of this study is to establish whether there is an association between eTT use and VTE. The primary objective of this study is to estimate the IRs and HR of VTE among a cohort initiating any testosterone products relative to a comparison group without testosterone replacement therapy. The secondary objective is to further estimate the crude and adjusted OR for the association between eTT and VTE in a nested case-control study setting to further evaluate eTT exposure related to VTE risk and confirm the findings from primary study design. All testosterone replacement products will be included in both primary and secondary analysis, as well as by different routes of administration including topical gel, transdermal patch, injection, and other testosterone products. The specific objectives to be assessed are as follows:

- **Primary Objective:** To evaluate the VTE risk using cohort study design by estimating the **incidence rates (IRs) and hazard ratio (HR)** of VTE among patients treated with testosterone replacement therapy (overall and by different routes of administration) relative to a propensity score matched untreated comparison group
- **Secondary Objective:** To evaluate the VTE risk using a nested case-control study within original cohort by estimating the **crude and adjusted odds ratio (OR)** of VTE for patients exposed to testosterone products (overall and by different routes of administration) compared to untreated patients

9. Research Methods

9.1. Study Design

The proposed study is comprised of 2 study designs: a retrospective cohort study proposed as a primary study design, and a nested case-control study as a secondary study to validate and confirm the findings from primary study design. The null hypothesis tested in the present study is that there is no increased VTE risk among testosterone-treated males, compared to untreated patients. It will also further explore the difference in the VTE incidence by different routes of administration. To achieve the study objectives, Truven Health Analytics MarketScan® (THAM) databases will be utilized without additional data acquisition.

The retrospective cohort observational study is proposed to utilize medical claims, pharmacy data, and enrollment information from electronic claims records in the United States to assess the crude and adjusted incidence rate of VTE among patients treated with any testosterone products and a cohort of hypogonadal patients without testosterone treatment matched to the treated cohorts on a propensity score estimated from baseline characteristics.

The treated cohort is composed of all patients who received at least 1 prescription for any testosterone products between December 2004 and December 2012 in the United States. The non-treated cohort consists of all hypogonadal patients who have no records of testosterone treatment claims in the database between December 2004 and December 2012. The primary comparison is the crude and adjusted incidence of VTE among hypogonadal patients as-treated with any testosterone relative to those propensity score matched non-treated patients. An additional analysis will be conducted to evaluate the association between VTE and testosterone exposure by different routes of administration, including topical gel, transdermal patch, injection, and nonspecific testosterone products. A new user design is used as a reasonable approach to reduce biases when the administrative healthcare database is used. In consideration of accounting for immortal time bias, person-time prior to exposure from the testosterone replacement therapy will be assigned to the reference group as unexposed person-time. **A nested case-control study** will be further performed to assess the association of testosterone exposure and VTE risk by estimating the crude and adjusted OR within the same hypogonadal cohort. For each VTE case, 4 controls without VTE will be selected from the same hypogonadal cohort regardless of eTT treatment matched to the cases on index date and age (± 1years). The event date for cases is the date of diagnosing VTE. Controls who did not receive a recorded VTE claim will be assigned a same event date as the cases to which they are matched. This study design has advantages for studying shortened/switching exposures and time-dependent variables. No chart abstraction is provided in the present study. Patients' characteristics and VTE risk factors including relevant medical and drug exposure information will be defined and compared between VTE cases and controls. The pattern of drug exposure will be categorized by current exposure and past exposure.

9.2. Study Setting

9.2.1. Study Population

The source population will consist of hypogonadal patients with at least **12 months (365 days)** of continuous enrollment in the health plan prior to index date. The medical claims will contain

at least 12 months of data proceeding cohort entry to characterize baseline variables for study subjects.

Inclusion criteria: Subjects are eligible for inclusion if they meet the following criteria:

- Males aged 18 years or older;
- Males with a hypogonadal condition;
    - Treated hypogonadal patients will be identified within the database who received at least 1 prescription for testosterone product. They are new users of testosterone treatment therapy who do not have usage during the baseline.
    - Untreated hypogonadal patients who had the diagnostic codes for hypogonadal conditions during a clinic visit but did not receive any testosterone prescriptions at this time will be identified as an initial comparison cohort.
- Continuous enrollment in the health plan (medical and prescription) for a minimum of 12 months prior to index date. Continuous enrollment will be defined as no enrollment gap exceeding 31 consecutive days at any given time in the course of the study.

Exclusion criteria: Subjects will be excluded from the study if they meet the following criteria:

- Female gender or dual gender
- Subjects with baseline VTE events

The hypogonadal condition will be defined as either a valid diagnostic code or a studied testosterone product, which is at least one of the following criteria:

- Prespecified diagnosis International Classification of Diseases, Ninth Revision (ICD – 9) codes

ICD 9 Code	***Descriptions***
257.2	Other testicular hypofunction
257.8	Other testicular dysfunction
257.9	Unspecified testicular dysfunction
758.7	Klinefelter's syndrome

- Prespecified approved testosterone products in the United States (Annex 6)

9.2.2. Testosterone Treatment Cohort

Treated hypogonadal patients will be identified within the database who received at least 1 prescription for testosterone product. They are new users of testosterone treatment therapy who do not have usage during the baseline. Because the cohort entry is based on the exposure status, the exposed subjects may have had the diagnosis that is used to define as the unexposed group prior to their exposure-defined index date. Immortal time bias occurs when valid testosterone person-time of follow-up with no testosterone exposure is not accounted for in the reference rate of VTE, resulting in an artificial increase in the rate of VTE in the reference group. To account for immortal time bias, the treated patients will be eligible as untreated prior to initiating testosterone treatment.

9.2.3. Untreated Cohort

Untreated hypogonadal patients will be defined as those who had a diagnostic code for hypogonadism and did not receive any testosterone prescriptions.

Treated and untreated cohorts will be balanced with regard to important baseline characteristics using propensity score matching methods.

9.2.4. Subgroup Study Cohort

Sub-cohorts among the testosterone-treated patient population will be identified based on the route of administration which are pre-determined products (details see Annex 6), including:

- Transdermal gel
- Transdermal patch
- Injection
- Nonspecific testosterone products

9.2.5. Propensity Score Matching

As medication cohorts were not formed by randomization but were observed based on usual care, comparisons between cohorts may be confounded by selection bias. To adjust for measured confounders, comparison between cohorts will be performed using propensity score matching method. The propensity score for each patient is defined by the predicted probability of testosterone initiation, given his measurable baseline characteristics (Schneeweiss et al. 2009). Details are provided in Section 9.7.1.1.

9.2.6. Nested Case-Control Study Population

To address the potential short duration of drug exposure, time-dependent confounders, and a drug utilization pattern that may involve short-term switching, a nested case-control study will be conducted within the original treated and untreated hypogonadal patients matched on propensity scores. This nested case-control study will include all cases of VTE events occurring within the original study cohorts. No chart validation will be performed to ascertain any additional information.

Cases and controls will be assessed for baseline characteristics and drug exposure patterns (no exposure, current exposure, or past exposure). To find controls with similar baseline covariate details to cases, the proposed study will sample the controls from cohort members with frequency matching up to a 4:1 control-to-case ratio with respect to age and index date to achieve an appropriate control group.

- The cases include all incident VTE cases within the original cohort comprised of both treated and untreated hypogonadal patients.
- The controls are non-VTE cases, 4:1 matching to VTE cases on age and index date.

9.2.7. Baseline Patient Characteristics

Baseline patient characteristics, including demographics, hospital utilization, VTE risk factors, comorbidities, and concomitant medications (Annex 7) will be compared between the testosterone-treated cohort and the non-treated cohort prior to propensity score matching. The detailed variables are listed in Section 9.3.3 below.

9.2.8. Study Period

9.2.8.1. Objective 1 Study

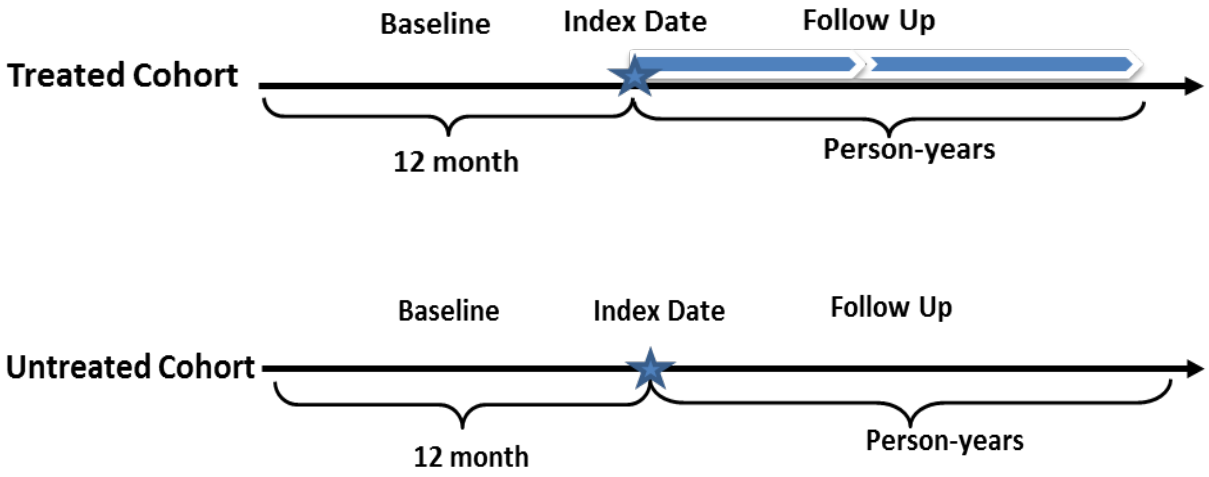
The retrospective cohort observational study will use medical records, pharmacy data, and enrollment information from claims records to assess the incidence of venous thrombotic events among patients treated with any testosterone product relative to a matched cohort of patients without testosterone treatment. The claims data in the United States will be retrieved from January 2004 to December 2012.

- Index date: For all participants in the study cohorts, the date of cohort entry will be marked as the index date, which is the beginning of observation for study outcomes. For treated patients, the index date is defined as the first prescription date of eTT. For the untreated patients, the index date is derived from the distribution of the number of days between the initial hypogonadal diagnosis and to prescription date of initial testosterone among the treated patients. The index date is selected at random and assigned to the non-users. Therefore, the overall distribution of the index date of the non-users matches that of the users' time for the first testosterone prescription. Non-users who had VTE before the assigned index date will be excluded from the analysis. This matched prescription time between testosterone users and non-users at cohort entry approach is considered a way to control for time-related bias (Zhou et al. 2005).
- Immortal time: The cohort entry is hierarchically based on the index date, which corresponds to the exposure status. Immortal time bias could occur when valid testosterone person-time of follow-up with no testosterone exposure is not accounted for in the reference rate of VTE, resulting in an artificial increase in the rate of VTE in the reference group. Thus, to control for such bias, the treated patients will be eligible as untreated prior to initiating testosterone treatment.
- Baseline time period: Baseline time period will be defined as the 12 months of continuous enrollment prior to the index date. For the purpose of this study, continuous enrollment will be defined as no enrollment gap exceeding 31 consecutive days at any given time in the course of the study.
- Drug exposure period: To account for switching, a primary analysis will be conducted in which exposure is defined as on-therapy measure (as-treated). In order to allow multivariate person-time analysis, all observation time in each subject will be classified according to all predictors simultaneously.
    - As treated: the period from the date of the last prescription plus 134 days, which is 30 days for prescription containing drug supply, plus an additional 14 days to account for refills, and plus an additional 90 days to allow the hemoglobin concentration and hematocrit to return to pre-treatment levels (Anderson et al.

1995). Prescriptions for testosterone products classified by the same route of administration that overlap within 134 days will be considered as 1 exposure period. The 90-day window is based on a previous study, which reported a 3-month recovery period to allow hemoglobin to return to pre-treatment levels. This approach is considered reasonable and was used by a previous study by taking into consideration of the fact that testosterone exposure may influence the future risk of developing VTE events after intake (Jick and Hagberg 2012).

In addition, initial cohort assignment (testosterone-treated or none treated), age, and all the covariates used in matching algorithm will be used to classify person time for the multivariate analysis. The primary analysis will be performed for treated versus non-treated.

- The end of follow-up for any given patient is based on: 1) the earliest of occurrence of a diagnosis of VTE (the date of diagnosis in the database), 2) disenrollment from health plan, 3) death, 4) end of the data availability, 5) end of current testosterone exposure for treated patients only, or 6) initiation of testosterone treatment for untreated patients only.



9.2.8.2. Objective 2 Study

The nested case-control observational study will be conducted using the original hypogonadal cohort. The VTE cases during the study period will be identified. The non-VTE control group will be matched to the case group on index date and age (±1 year).

- The event date for VTE cases will be defined as the date when the VTE event occurred. Controls who did not receive a recorded VTE claim will be assigned a same event date as the cases to which they are matched.
- The pattern of drug exposure will be categorized by no exposure, current exposure, and past exposure.
    - Current exposure is defined as the start date of the claim for a testosterone prescription until the last prescription plus 30 days to allow prescription supply

plus 14 days (to allow for drug non-adherence), and plus 90 days (to allow hemoglobin/hematocrit return to pre-treatment level), where the exposure overlaps the event date.

- Past exposure: the exposure history will be calculated based on the total number of testosterone prescriptions claimed in the 134 days prior to the event date.

9.2.8.3. Drug Switching

Generally, testosterone drug switching between classes is not common. Factors leading to drug switching in the preparation include cost, side effects (rash--only 7%-10% for gels), and variations in serum testosterone levels (which are quite common with transdermal gels). Otherwise, generally, switching is not substantial. For the primary analysis of treated patients, the switchers between testosterone products will not affect the analysis. While in the analysis of patients treated with different formulary testosterone products, the person time will not be accumulated if the patients switched to another study testosterone with a different route of administration. For example, if a patient initially received a 90-day prescription for an injectable testosterone and then switched to a testosterone gel solution 4 months after, he will be considered exposed only to an injectable testosterone. The patient's exposure time on the testosterone gel solution will not be counted in the analysis and he will be censored at the time of drug switch. The study utilizes a new user design as a reasonable strategy to reduce bias when healthcare databases are used (Johnson et al. 2012).

9.3. Variables

9.3.1. Exposure Variable

The exposure variable is testosterone replacement therapy, and will be categorized by any testosterone use or pre-specified routes of administration: transdermal gel, transdermal patch, injection, and non-specific testosterone use. The different formulations of testosterone are considered as proxy variable for dose response, injectable testosterone as the highest concentration of testosterone followed by transdermal patch and gel. The study drugs are listed in (see Annex 6).

9.3.2. Study Outcome

The study outcome is incident VTE, which combines DVT and PE. All incident VTE will be identified in the database after initiation of the drug and within the follow-up positive exposure period. According to the FDA Mini-sentinel project, a systematic review of validated methods for identifying VTE revealed the use of ICD-9 codes 415.x, 451.x, and 453.x are appropriate for identification of VTE in claims databases, which yields the highest positive predictive value (PPV) (65%-95%) across studies. It has been reported that PPV was higher for studies using the combined event like VTE than when each specific event was examined (Tamariz et al. 2012).

Furthermore, the study is aimed to evaluate drug-induced VTE, thus using idiopathic VTE cases by excluding other proxy factors such as trauma, injury, and hospitalization could be a reasonable approach. However, because of the nature of the claims database, it is difficult to develop an algorithm that will accurately distinguish between idiopathic and non-idiopathic VTE

cases without chart validation. Thus, a practical definition is to categorize VTE cases, following an adjudication process.

- Non-idiopathic (secondary) VTE is defined as VTE cases associated with at least 1 of the following well-established risk factors: hospitalization stay of more than 3 days, fracture of lower limb, major surgery, and cancer diagnosed within 3 month of VTE occurs.
- Idiopathic VTE is defined as VTE cases without any of risk factors listed for non-idiopathic VTE.

Adjudication process: The claims of diagnoses, procedure and prescription 3 months prior and 1 month post the VTE event date will be reviewed and adjudicated by 3 independent clinicians from Lilly medical department with experience in VTE diagnosis and treatment, blinded to study drug exposure. Two adjudicators will review the claims history and determine whether each VTE case is idiopathic or not. If there is a conflict opinion, a third adjudicator will be involved. The final decision on a case will be decided by majority. This approach will decrease the likelihood of misclassification of idiopathic, non-idiopathic VTE cases, or inclusion of non-cases. If needed, anti-coagulation treatment will be considered to add into the definition.

9.3.3. Baseline Characteristic Variables

Baseline characteristics will include demographics, resource utilization, comorbidities, VTE risk factors, and common medication use.

Demographics:

- Age (at index date)
- Prescriber specialties (urology, endocrinologist, general practice, others, unknown)
- Year of index date
- Total testosterone level (ng/dL) (if applicable)

Resource Utilization

- Inpatient stay (count: days)
- Emergency Department visit (count: days)
- Outpatient/other visit (count: days)
- Number of different ICD-9 codes (first 3 digits) (N)
- Number of prescriptions by therapeutic class (N)

Charlson Comorbidities

- Charlson Comorbidity Index
- Myocardial infarction

- Congestive heart failure
- Peripheral vascular disease
- Cerebrovascular disease
- Dementia
- Chronic pulmonary disease
- Rheumatologic disease
- Peptic ulcer disease
- Mild liver disease
- Diabetes
- Diabetes with chronic complications
- Hemiplegia
- Renal disease
- Lymphoma
- Moderate liver disease
- Metastatic solid tumor

Pre-selected Conditions (Annex 4)

- Hypogonadism
- Erectile dysfunction
- Klinefelter's syndrome
- Sleep disturbance
- Malaise or fatigue
- Pituitary disorders
- Testicular cancer
- Prostate Disease
- Prostate cancer
- Thyroid disease
- Osteoporosis
- Major fracture
- Depression

- Cognitive impairment
- Chronic obstructive pulmonary disease
- Asthma
- Baseline VTE

Concomitant Medication (Annex 7)

- Antihyperlipidemics (Antilipemics)
- Antihypertensives
- Diabetes – agents to lower blood sugar
- Erectile dysfunction
- Hematological agents
- Opiates
- Psychotropics
- Sleep medications

9.3.4. VTE Risk Factors (based on literature and database availability)

The VTE risk factors will be categorized by non-modifiable risk factors, modifiable/acquired risk factors, and temporary risk factors as follows (Annex 5). The temporary risk factors will be assessed both at baseline and 30 days prior to the event date:

- Non-modifiable risk factors:
    - Age
    - Genetic/congenital factors (primary hypercoagulable state: factor V Leiden mutation, antithrombin III deficiency, etc.)
    - Inherited hypercoagulable syndrome
- Modifiable factors:
    - Cancer/cancer treatment
    - Metabolic disorder
        - Hypertension
        - Hypercholesterolemia
        - Diabetes
        - Obesity
    - Chronic Renal Disease
        - End-stage renal disease

  - Cardiovascular Disease
    - Myocardial infarction
    - Ischemic stroke
    - Heart failure
  - Varicose vein
  - Rheumatoid arthritis
  - Infection
  - Inflammatory bowel disease
- Temporary risk factors
  - Hip fracture or other lower limb injury
  - Major surgery
  - Hospitalization

9.4. Data Sources

The present study will utilize a US-based electronic claim database: THAM database.

9.4.1. Truven Health MarketScan® Research Databases

Truven Health Analytics MarketScan ® (THAM) Databases contain individual-level, de-identified, healthcare claims information from employers, health plans, hospitals, Medicare, and Medicaid programs. Since their creation in the early 1990s, the THAM databases have grown into one of the largest collections of de-identified patient-level data in the nation. These databases reflect the real world of treatment patterns and costs by tracking millions of patients as they travel through the healthcare system offering detailed information about all aspects of care. Data from individual patients are integrated from all providers of care, maintaining all healthcare utilization and cost record connections at the patient level. Used primarily for research, these databases are fully Health Insurance Portability and Accountability Act (HIPAA) compliant. Research using THAM data has been widely publicized in peer-reviewed journals. In the most recent full data year, MarketScan claims databases contain data on 50 million covered lives. Its sample size is large enough to allow creation of a nationally representative data sample of Americans with employer-provided health insurance and Medicaid.

9.4.2. Database Major Limitations

Truven Health Analytics MarketScan ® (THAM) databases provide an opportunity for research purposes. As with any data source, these databases have limitations. Some of the limitations result from data structure and others are due to the sample population. Key common limitations include the followings:

- Lack of clinical details makes it hard to verify the validity of diagnosis codes and to refine statistical analyses. Data on important confounding variables (smoking, alcohol use, body weight, and height) are not available in the claims database.
- Diagnoses, medical procedures, and medicine dispensing will not be captured if no corresponding billing codes were generated. Likewise, the use of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, current procedural terminology codes, or national drug codes is subject to the incompleteness or inaccuracies of the coding in the database;
- MarketScan claims databases are based on a large convenience sample. The data come mostly from large employers; medium and small firms are not represented. Because the sample is not random, it may contain biases or fail to generalize well to other populations.
- Only prescribed medicines are recorded in the database. No information about over-the counter drug (e.g., aspirin) use is available.

9.5. Study Size

Feasibility assessments to determine the sample size and study power have been conducted, and the study power is anchored using the primary retrospective cohort study design.

To derive the sample size estimation for the retrospective cohort study, it is assumed that the incidence rate of VTE in the reference group (un-treated) is 15 per 1000 patients. We further assumed the difference between the treated group and reference group is 10 per 1000. With these assumptions, we will require **3229** patients to detect a statistical significance in the incidence rate of VTE between groups, with approximately 80% power. A query of the THAM database finds there are in excess of 200,000 unique patients with at least 1 prescription of any testosterone replacement therapy (see Annex 8).

Table 1. Power and Sample Size Estimation of Primary Retrospective Cohort Study

	Power = 1- β (type II error)			
Difference in incidence rate (per 1000)	60	70	80	90
1	151,458	190,314	241,478	322,597
5	7101	8844	11,140	14,779
10	2089	2581	**3229**	4256
15	1064	1307	1626	2132
20	673	823	1019	1331
25	478	582	718	934

*Assumptions:

1) alpha= 0.05, beta= 0.20
2) Crude incidence rate of VTE in reference group is 15 per 1000 person-years.

In addition, in order to derive the sample size for the nested case-control study, the following assumptions were made: 1) the proportion of the control group that we expected to be exposed is 0.50; 2) the ratio of the controls to cases is 4:1; 3) the expected OR is 2.0. To achieve 80%

power, the study will need to enroll 88 VTE cases and 352 non-VTE cases (see Table 2). The preliminary data showed that THAM databases contains >200,000 patients; given the incidence rate of VTE is 1 per 1000, the study is expected to have sufficient patients with VTE outcome in the original hypogonadal cohort.

Table 2. Power and Sample Size Estimation of Secondary Nested Case Control Study

	Power = 80% (type II error)	
OR	Cases	Controls
1.1	4,327	17,308
1.5	245	980
2.0	**88**	**352**
2.5	54	216

Assumptions:

1) alpha= 0.05, beta= 0.20
2) The proportion of the control group that is expected to be exposed is 0.50.
3) The ratio of the controls to cases is 4:1.
4) The expected OR is 2.0.

9.6. Data Management

SAS (r) Proprietary Software 9.2 will be utilized for data management; the relevant comments such as *proc datasets, proc format, proc sql* etc. will be used to access the raw data, manage the analytical dataset, and process the integrated analytical datasets. Datasets and analytic programs will be kept on a secure server and archived per Lilly record-retention procedures.

9.7. Data Analysis Plan

9.7.1. Objective 1 Study: Retrospective Cohort Study

The primary analysis of this protocol is to compare VTE risk between treated patients versus untreated patients using a Cox proportional hazard model. The study cohorts will be matched on propensity scores.

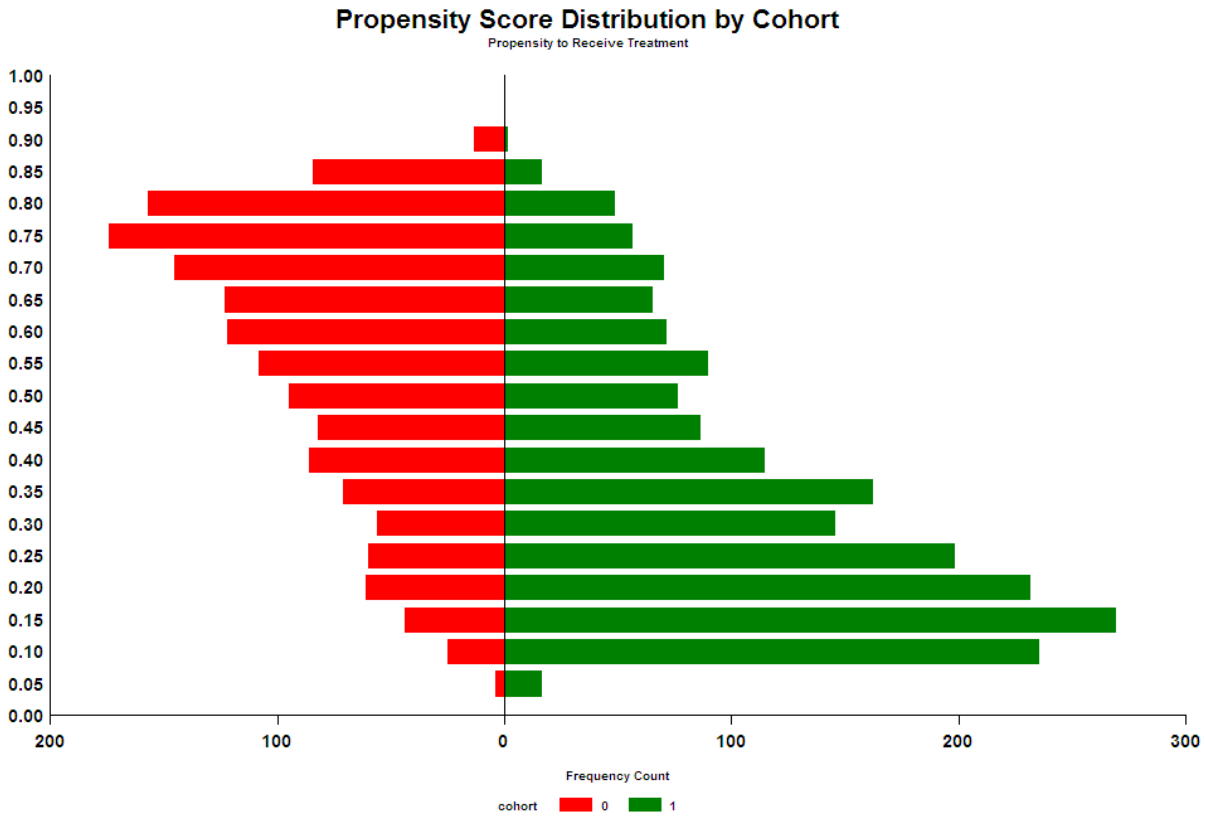
9.7.1.1. Propensity Score Estimation

Estimate propensity score

The propensity score for each patient is defined by the predicted probability of testosterone initiation, given their measurable baseline characteristics (Schneeweiss et al. 2009). No post-baseline or outcome information will be used in this step of the analyses. By using only pre-treatment characteristics in the propensity score modeling, the comparison groups can be formed independently of any outcome information. The propensity score will be estimated using logistic regression, with cohort (the treated or untreated) as the outcome variable. The logistic regression propensity model will include the following terms as independent variables: pre-identified baseline characteristics among the testosterone users and non-users listed in Section 9.3.3 and Section 9.3.4. The interaction term or nonlinear terms for continuous variables will also be considered. To account for potential calendar time trends in testosterone prescribing, propensity

models will be developed within 6-month blocks from December 2004 to June 2012. Propensity score estimated using the entire cohort (treated or untreated) will be applied to the subsequent subgroup (transdermal gel, transdermal patch, injection, and unspecific testosterone use) analysis, and this approach was proved to be a reasonable approach (Rassen et al. 2012).

As discussed in a later section, the balance between cohorts achieved using the above model will be assessed and the need for additional variables, interactions, or non-linear terms, or a reduction in terms, may be assessed by examining baseline data relationships with potential confounders and cohort (though not with outcome of interest). However, the propensity score model will be finalized prior to initiating the analysis of the study outcome measure. The distribution of the estimated propensity scores for each cohort will be summarized as illustrated in Example Figure 1.



Example Figure 1. Side-by-side histograms of propensity scores for cohorts: testosterone-treated cohort and untreated cohort.

High dimension propensity score

In addition, the selection of the additional variables for the propensity score model will be referenced as the modified High dimensional propensity score model which is recommended by Schneeweiss et al (2009). These variables will be ranked based on the absolute value of log transformation (Bias Risk index). Prevalence and bias index will be calculated for these additional variables. The low prevalence and/or low bias index variables will be excluded in the

propensity score model. The calculation of the bias index will be using the following formula. The propensity score analyses will be adapted from the OMOP-developed SAS macros for High Dimension Propensity Score analysis published at the OMOP website http://omop.fnih.org/MethodsLibrary.

$$Bias_m = \frac{P_{C1}(RR_{CD} - 1) + 1}{P_{C0}(RR_{CD} - 1) + 1}, \text{if } RR_{CD} \geq 1$$

$$Bias_m = \frac{P_{C1}\left(\frac{1}{RR_{CD}} - 1\right) + 1}{P_{C0}\left(\frac{1}{RR_{CD}} - 1\right) + 1}, \text{if } RR_{CD} < 1$$

P_{C1}: prevalence of a binary confounding factor among exposed subjects;

P_{C0}: prevalence of binary confounding factor among unexposed subjects;

RR_{CD}: independent association between a confounder and the study outcome.

Propensity score matching

Testosterone initiators will be 1:1 matched to untreated cohort patients on the estimated propensity score of receiving testosterone treatment. Matching will be performed using a standard matching algorithm - a greedy 1:1 matching algorithm (D'Agostino 1998) will be utilized to match each treated patient with an appropriate control patient in the untreated cohort. The algorithm will utilize ranked-based Mahalanobis distance (or absolute value of differences in propensity score) with a caliper of 0.2 standard deviations of the logit of the propensity score (Austin 2010; Rosenbaum 2010). The propensity stratification method will be used as a sensitivity analysis. These analyses will be performed using SAS.

Evaluation of quality of propensity score adjustment

Prior to initiating the outcome analysis, the quality of the propensity score adjustment and associated assumptions will be evaluated. The appropriateness of the propensity score modeling is judged by whether balance on pretreatment characteristics is achieved between the treatment and control groups (D'Agostino and D'Agostino 2007; Rubin 2007). The balance produced by the propensity scoring will be assessed by significance testing, assessment of standardized differences (both of which assess differences in means between the 2 cohorts), and assessment of the distribution of each covariate between cohorts (Austin 2006).

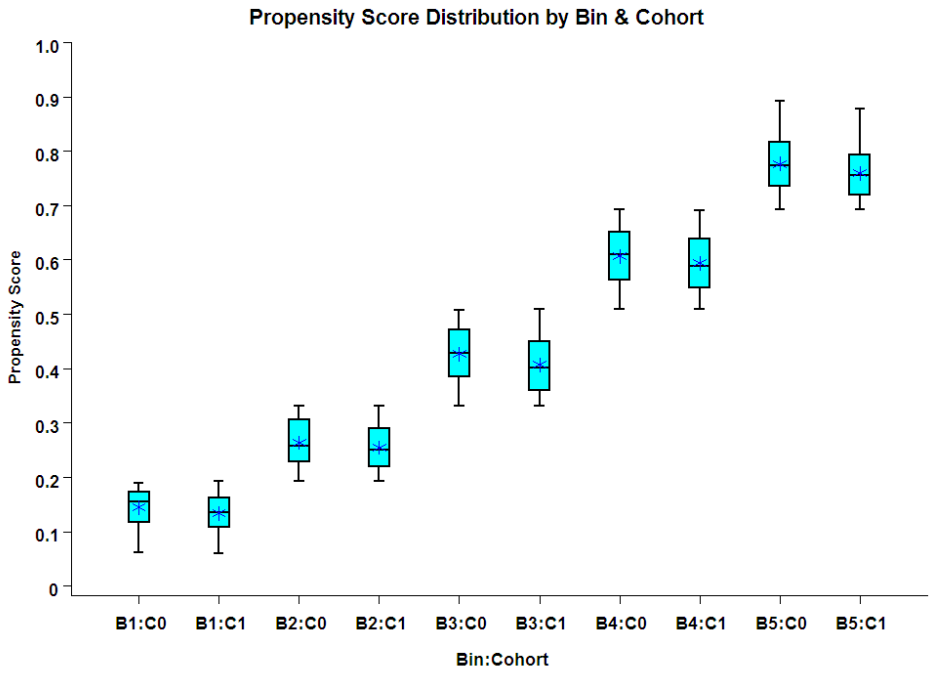
For Propensity Score Matching: First, t-tests and Chi-square tests will be utilized to assess differences between the cohorts across all measured baseline covariates before and after propensity matching (see Example Table 3). In addition, the standardized differences, defined as the difference in means between the 2 groups divided by a measure of the standard deviation of the variable, will be computed and displayed (see Example Figure 2). Standardized differences can be computed for both continuous and binary covariates and can identify specific covariates with larger residual imbalances after propensity score adjustment. As a rule of thumb,

standardized differences greater than 0.10 indicate imbalance that may require further investigation (Austin and Mamdani 2006).

Example Table 3. Balance Assessment Using Significance Testing: Summary of Cohort Differences Before and After Propensity Score Matching

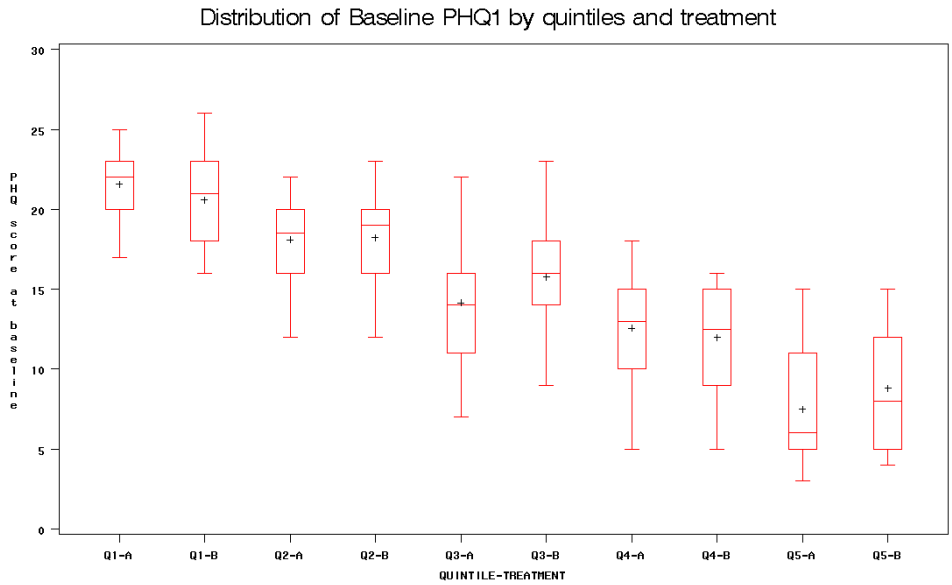
		Full Sample				Matched Sample		
		Cohort A	Cohort B			Cohort A	Cohort B	
		(N =)	(N =)	p-value		(N=)	(N =)	p-value
Age, mean (sd)								
Female, %								
…		…	…	…		…	…	…

Abbreviation: sd = standard deviation.



Example Figure 2. Distribution of propensity scores by cohort and strata.

As opposed to significance testing and standardized differences, which assess differences in means, side-by-side box plots (or histograms) may be used to investigate the similarity in the full distributions of key continuous covariates between the treatment cohorts (see Example Figure 3). This assessment of the distributions will help in detection of violations of the positivity assumptions.



Example Figure 3. Distribution of key covariate (baseline PHQ1) by PS strata and cohort.

9.7.1.2. Outcomes Analysis

There may be significant differences in pre-treatment risk factors among the 2 treatment groups and these differences may contribute to any observed differences in outcome measures. In order to control for the potential confounding due to pre-treatment risk factor imbalances among groups, propensity score analyses will be used to find comparable groups for analysis of outcomes as described in Section 9.3.2. The treated and untreated subjects will be matched based on propensity score in a 1:1 ratio, and a greedy 1:1 matching within caliper method will be used. The baseline characteristics of the matched cohorts will be presented to show the balance in the baseline characteristics after matching. The baseline characteristics for the pre-matched population will also be presented. Summary of baseline characteristics will also be presented for those subjects who are not included in the propensity score-matched analysis. An exploratory analysis on lab measurement of total testosterone level will be assessed to display any difference in pre-treated testosterone level between treated and untreated groups during the pre-index date period. Given that the lab measurements in Marketscan are not representative of the entire cohort, the analysis remains descriptive and will be interpreted in light of the data limitations. Another descriptive analysis will be performed to show if there are any differences in VTE temporary risk factors (see Section 9.3.4) between treated and untreated cohorts post-index date.

Cox regression model will be used for the time-to-VTE analysis. The start date is the index date. The censored date for the treated subjects is the end of the at-risk period (defined in Section 9.3.1) or the last database enrollment date of the subjects, whichever comes first. The censored date for the untreated subjects is the date of last database enrollment date for the subject. The Cox regression model will include treatment, age at index, index date, baseline patient characteristics, and VTE risk factors that did not reach balance between the 2 arms after propensity score matching as independent variables. For the comparison of VTE in treated and

untreated groups, the incidence rate of VTE will be calculated for each group, and the hazard ratio with 95% confidence interval and p value will be reported. Multiplicity is not considered in this analysis. Diagnostics will be conducted to assess the proportionality assumption for the Cox regression models in the analyses. If required, a modification to the models to accommodate departures from proportionality of the hazards will be executed (e.g., stratified partial likelihood estimation). Furthermore, a time-dependent variable will possibly be considered to modify the model if there is an interaction between the transit VTE risk factor and time. Due to consideration of over fitting the model when adding time-dependent variables, the decision will be made based on strong scientific evidence from the descriptive analyses.

9.7.2. Objective 2 Study: A Nested Case Control Study

Cases and controls will be assessed and characterized based on baseline characteristics listed in Section 9.3.3 and any important VTE risk factors listed in Section 9.3.4, the differences of baseline characteristics will be compared between cases and controls by 2 sided t-test, the significance level will be set at 0.05. The exposure pattern will be evaluated to address the possibility of short-term use of testosterone medication or drug switch due to short duration and time-varying confounding factors. The exposure will be categorized into no exposure, current exposure, and past exposure. A descriptive analysis will be performed between VTE cases and controls on all baseline characteristic variables and VTE risk factors. The difference will be calculated by t-test or analysis of variance with a significance level at 0.05.

Conditional logistic regression will be used to estimate the association between testosterone use and VTE. The association between testosterone exposure patterns (current and past exposure to testosterone medication) and VTE risk will be reported as an adjusted OR representing the testosterone exposures relative to non-testosterone users.

- A stepwise selection will be used to screen the pre-determined variables to improve the discrimination of the model. The stepwise criteria will be p-value of 0.20 for model entry and 0.10 for retaining variables. Variable selection process will take into account both statistical significance and clinical meanings. All baseline characteristic variables and VTE risk factors will be evaluated and compared between cases and controls.
- A conditional logistic regression will be used to obtain the adjusted OR that accounts for all the statistically significant and clinically meaningful variables in addition to age at index and calendar year of index. The significance level will be set at 0.05. The analyses will be performed using SAS.

9.7.3. Sensitivity Analysis

A variety of sensitivity analyses will be conducted in this study to evaluate the robustness of the findings.

Sensitivity analysis given different outcome groups: Given the nature of claims database, it is impossible to differentiate idiopathic VTE from non-idiopathic VTE cases without further reviewing the medical charts. The present study will evaluate all VTE cases and stratify by idiopathic VTE and non-idiopathic VTE cases. A sensitivity analysis will be performed to

evaluate the impact of different definition for idiopathic VTE by using different diagnostic or procedure codes.

Sensitivity analysis given different exposure period (at-risk time period): For both the retrospective cohort and nested case-control study, the as-treated analysis will be used. The drug use/exposure will be categorized into current use/exposure and past use/exposure. Ninety days will be used as the period in which to allow the drug-induced elevated risk to return to the pretreatment level. To be more conservative, a sensitivity analysis will be performed to evaluate the risk when the patient is exposed to testosterone without 90 days. This sensitivity analysis will adequately evaluate the recent drug-utilization pattern and the impact of using different at-risk time periods.

Sensitivity analysis with unmeasured confounding: While the propensity adjustment utilized in the primary analysis accounts for bias in measured confounders, the potential for bias from unmeasured confounders remains. While one cannot test for the presence of unmeasured confounding, the plausibility can be examined by utilizing baseline data to see if measured covariates can explain the differences between cohorts on the baseline score of the outcome measure (Haviland et al. 2007). A sensitivity analysis will be performed to address the potential impact of unmeasured characteristics between hypogonadal patients due to different causes. While the primary analysis explores patients with all related hypogonadism diagnostic codes, a sensitivity analysis will exam whether certain hypogonadal diagnostic codes, for example, Klinefelter's syndrome (KS), will impact the primary results due to the unmeasured differences in patients' characteristics. The regression model will be run with and without a KS diagnostic code to assess the impact on the results. Therefore, a sensitivity analysis will define the magnitude of potential spurious effects on observed study associations potentially accounting for unmeasured confounding factors.

Other sensitivity analyses may be performed during the propensity score model development. This may involve evaluating certain covariates and their impact on the propensity score model development. A 1:1 matching method is the primary method for outcome analysis and the stratification method will be used as sensitivity analysis.

9.8. Quality Control

The study will use an existing database, which have been used primarily for research, fully HIPAA compliant. The study programs for data management or statistical analyses will be dual validated by 2 individuals to ensure data integrity and accuracy. All study programs, log files, and output files will be stored on the secure sever, and archiving any statistical programming performed to generate the results. In addition, VTE cases would be adjudicated by 3 experienced clinicians to ensure the accuracy of the diagnosis and decrease the misclassification.

9.9. Limitations of the Research Methods

The current study adopts an existing propensity score methodology and OMOP-developed macros to identify a comparison group that is comparable with regard to the elevated risk of drug induced VTE. This approach offers robust control for confounding because it enables tailoring of the covariates selection based on pre-treatment characteristics of testosterone users and the event

of interest. This study utilizes both the cohort study and nested case-control study design to comprehensively evaluate the association between testosterone use and the elevated risk of VTE through adjusted IR, HR, and adjusted OR.

However, this study does have limitations. While claims data are extremely valuable for the efficient and effective examination of disease outcome and treatment patterns, claims data are collected for the purpose of payment and not research. Therefore, there are limitations associated with the use of claims data.

I. **First,** the presence of a claim for a filled prescription does not indicate that the medication was consumed or that it was taken as prescribed.

II. **Second,** the presence or absence of disease may not be accurate, as the diagnostic code may be incorrectly coded or included as rule-out criteria rather than actual disease.

III. **Third,** several important covariates are missing in the claims database such as body weight, genotypes for inheritable hypercoagulation condition such as protein C deficiency, protein S deficiency, factor V Leiden, prothrombin G20210A, etc. However, the study did include a number of pre-treatment covariates in the propensity score model to balance and minimize the differences between treated and untreated cohorts.

IV. **Fourth,** the study outcomes are not validated through chart validation. Certain clinical and disease-specific parameters will not be readily available in claims data. For example, it is difficult to accurately differentiate idiopathic and non-idiopathic or secondary VTE cases. The proxy causes of VTE such as trauma, injury, extended hospitalization, and cancer may not be completely captured in claims database. It is difficult to determine a scenario if a VTE occurred due to a hospitalization or vice versa. Such misclassification of idiopathic and non-idiopathic VTE cases would potentially dilute the association between drug effect and the VTE risk. However, we require all VTE cases being reviewed independently by 3 clinicians to be blinded by the exposure status, which will decrease the likelihood of misclassification.

V. **Fifth,** the information on lab measurement is not completely available in claims data. The surveillance bias may exist if the patient treated with testosterone replacement therapy are routinely monitored for certain disease conditions, such as increased hematocrit or hemoglobin level or are diagnosed more frequently with polycythemia (as noted in the medication guides or package inserts of most of testosterone medications). In addition, due to the incomplete lab measurement on total serum testosterone, the treated and untreated cohorts will not be able to be matched on the level of total testosterone level (TT). The selection bias could be introduced if the untreated cohort has higher TT levels compared to the treated cohort, which could be potentially related to disease severity. However, the serum testosterone level was reported not to be related to VTE risk and propensity-score matching the untreated cohort to the treated cohort on a number of pre-treatment covariates will help to minimize the differences between the cohorts.

9.10. Other Aspects

None

10. Protection of Human Subjects

All information about this observational study and individual medical information resulting from this study are considered confidential, and disclosure to third parties is prohibited except for regulatory authorities and as applicable by law. This study will be conducted in accordance with applicable laws and regulations of the United States, where the study is being conducted, as appropriate.

11. Management and Reporting of Adverse Events/Adverse Reactions

During the course of retrospective observational research, the proposed study will not involve chart validation to obtain extra information on adverse events. Thus, Lilly is not expecting to report any adverse events or reactions.

12. Plans for Disseminating and Communicating Study Results

The study will be registered in EU EnCepp Registry and the study findings may be presented in a scientific congress and submitted to a peer-reviewed journal.

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Annex 1. List of Standalone Documents

No.	Document Reference No	Date	Title
1.	Annex 1	26 September 2013	List of standalone documents
2.	Annex 2	26 September 2013	Diagnostic Codes for hypogonadism
3.	Annex 3	26 September 2013	Diagnostic Codes for VTE
4	Annex 4	26 September 2013	Diagnostic Codes for prespecified comorbidities
5	Annex 5	26 September 2013	Diagnostic Codes for VTE risk factors
6	Annex 6	26 September 2013	List of Testosterone products by routes of administration
7	Annex 7	26 September 2013	List of Concomitant Medication
8	Annex 8	30 September 2013	Feasibility assessment and patients' baseline characteristic study: Abstract published in ISPE2013