A PHASE 1, OPEN-LABEL, RANDOMIZED, 2-TREATMENT SINGLE-DOSE, CROSS-OVER STUDY, 2-PART DESIGN TO EVALUATE THE BIOEQUIVALENCE AND TOLERABILITY OF TESTOSTERONE CYPIONATE FOLLOWING INTRAMUSCULAR (IM) INJECTION IN HEALTHY HYPOGONADAL MALE SUBJECTS

Investigational Product Number:	PF-03745638
Investigational Product Name:	Testosterone cypionate
United States (US) Investigational New Drug (IND) Number:	Not Applicable (N/A)
European Clinical Trials Database (EudraCT) Number:	Not Applicable (N/A)
Protocol Number:	B5341002
Phase:	1

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment #3	06 August 2019	• Section 4.2 Screening supine systolic blood pressure 90-150 mm Hg (inclusive) or diastolic blood pressure 50-95 mm Hg (inclusive), following at least 5 minutes of supine rest. If blood pressure is ≥150 mm Hg (systolic) or ≥95 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the subject's eligibility. Rationale: More variability in the blood pressure in hypogonadal population.
Amendment #2	18 July 2019	• Title changed to remove 2-Period. A corresponding change was also made in all applicable areas. Rationale: in Part 1, there are 2 periods and in Part 2, there are 3 periods. [redacted] • Duration of subject participation Part 2 updated based on the new design (Protocol Summary, Section 3, Study design): each subject will participate in the study with the duration of approximately 25 weeks from the time the subject signs the informed consent form through the

Document	Version Date	Summary of Changes and Rationale
		final contact/follow up contact. This includes a screening phase up to 4 weeks (28 days), ~16 weeks for dosing assuming, 45 days between treatments and up to 5 weeks for follow up contact. • Addition of footnote "b" of SOA table to specify the updates applicable to only Part 2. • A window of no more than 2 hours is allowed (ie, 6-8 am) for sampling the predose samples. • Rationale: Language from Protocol Administrative Change Letter issued 4th April 2019 included in Protocol Summary, SOA and Section 7.2.1. • Section 7.3 blood volume was updated to 306 mL. Rationale: Due to the addition of 3rd period additional blood samples will be collected for estimating testosterone and DHT. • Other typographical and editorial errors were corrected throughout the document for clarity.
Amendment #1	11 Dec 2018	CCI [redacted] • Addition of footnote "b" of SOA table to specify baseline serum testosterone needed. Rationale: clarification for inclusion/exclusion criteria.

Document	Version Date	Summary of Changes and Rationale
		CCI [redacted] • Change of hypogonadal male serum testosterone from 300 ng/dL to 250 ng/dL in Study rationale (1.3.1). Rationale: Fix typographical error. • Change from Day 20 to Day 21 in SOA Table and Study overview (3.1). Rationale: to align with 480 hours. CCI [redacted] • A full physical exam will be performed in Period 2, Day -1 in SOA table and. "Limited" changed to "full" in Subject Withdrawal (6.4). Rationale: Both changes to account for full physical for safety. CCI [redacted]

Document	Version Date	Summary of Changes and Rationale
		CCI [redacted] • Addition of "PSA" in Safety Laboratory Tests (Table 3) under "other." Rationale: add clarity and synchronize with text. • Other typographical and editorial errors were corrected throughout the document for clarity.
Original Protocol	15 May 2018	• Not applicable (N/A).

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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APPENDICES

PROTOCOL SUMMARY

The current presentation of testosterone cypionate solution for injection is highly concentrated (supersaturation) with respect to the active pharmaceutical ingredient (API) and therefore makes the product susceptible to crystallization when exposed to lower temperatures than recommended on the approved label [20°C to 25°C (68°F to 77°F)]. Currently the 200 mg/mL United States Prescribing Information[1] (USPI) include "Warming and shaking the vial should re-dissolve any crystals that may have formed during storage at temperatures lower than recommended". To avoid crystallization and maintain true solution properties, the 200 mg/mL formulation is being modified to improve the solubility of the active ingredient in the vehicle. The current study will be assessing the bioequivalence (BE) and tolerability between the currently approved formulation and the reformulated presentation of testosterone cypionate solution for injection.

This is an open-label, randomized, 2-treatment, single-dose, cross-over study, 2-part design to evaluate the BE and tolerability of testosterone cypionate solution for intramuscular (IM) injection in healthy hypogonadal male subjects (ages of 18 to 65 years).

The objectives and endpoints of this study are listed below.

Part 1	
Primary Objective:	**Primary Endpoints:**
• To estimate the exposure variability of the test and reference formulations of testosterone cypionate solution for injection (200 mg) given intramuscularly as a single dose.	• AUC_{last}, AUC_{inf}, and C_{max} of total testosterone (baseline corrected).
CCI [redacted]	[redacted]

Part 2	
Primary Objective:	**Primary Endpoint(s):**
• To evaluate the BE of the new formulation (testosterone cypionate solution for injection; 200 mg) relative to the currently marketed formulation (testosterone cypionate solution for injection; 200 mg) administered intramuscularly as a single dose.	• AUC_{last}, AUC_{inf} (if data permit), and C_{max} of total testosterone (baseline corrected).
CCI [redacted]	[redacted]

In Part 1, approximately 12 subjects will be enrolled to ensure 10 evaluable subjects in the study. Subjects will be randomized according to a computer-generated randomization schedule to receive the following 2 treatments below in random order.

Treatment A:

A single testosterone cypionate solution for injection (new formulation) 200 mg dose administered IM deep in the gluteal muscle (Test formulation).

Treatment B:

A single testosterone cypionate solution for injection (currently marketed formulation) 200 mg dose administered IM deep in the gluteal muscle (Reference formulation).

In Part 2, approximately 60 subjects will be enrolled to ensure 57 evaluable subjects in the study. In Part 2, the variability associated with maximum observed concentration (C_{max}) and area under the curve (AUC) as well as the point estimates obtained from Part 1 were to be used to inform the sample size needed to attain BE.

Subjects will be randomized according to a computer-generated randomization schedule to receive the 2 treatments (eg, same as listed in Part 1) in a random order.

For Part 1, each subject will participate in the study with the duration of approximately 19 weeks from the time the subject signs the informed consent form through the final contact/follow-up contact. This includes a screening phase up to 4 weeks (28 days), ~10 weeks for dosing assuming, 45 days between treatments and up to 5 weeks for follow-up contact.

For Part 2, each subject will participate in the study with the duration of approximately 25 weeks from the time the subject signs the informed consent form through the final contact/follow-up contact. This includes a screening phase up to 4 weeks (28 days), ~16 weeks for dosing assuming, 45 days between treatments and up to 5 weeks for follow-up contact.

For each Part separately, natural log transformed area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (AUC_{last}), area under the plasma concentration-time profile from time zero extrapolated to infinite time (AUC_{inf}) (if data permit) and C_{max} of total testosterone (baseline corrected [mean of the 4 predose measurements] and uncorrected) will be analyzed separately using a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (Test – Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios.

For each Part separately, pharmacokinetic (PK) concentrations and parameters will be listed, summarized descriptively and graphed per sponsor standards.

If results from Part 1 depict within-subject variability ≥30% (eg, highly variable drug), the study design and/or methodology of data analysis may be modified.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1. Schedule of Activities

Visit Identifier[a]	Screen		Periods 123[b] (45 day washout in between drug administration)																
		Day -1	Day 1						Day 2		Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 11	Day 15	Day 21	Follow-up*
Hours Post Dose			**-1**	**-0.5**	**-0.25**	**0**	**1**	**8**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	**168**	**240**	**336**	**480**	
Informed consent	X																			
CRU confinement		X	→	→	→	→	→	→	→	X										
Inclusion/exclusion criteria[c]	X	X																		
Medical history	X	X																		
Alcohol breath test or alcohol blood test[d]		X																		
Physical examination	X	X[e]																	X[f]	
Safety laboratory	X	X																		
Demography	X																			
Height and weight	X																			
Contraception check[g]	X	X									X	→	→	→	→	→	→	→	X	
Urine drug testing	X	X																		
PSA test and rectal examination	X																		X	
ECG	X		X																X	
BP and pulse rate	X	X																		
HIV, HepBsAg, HepBcAb, HCVAb testing	X																			
Study treatment administration						X														
PK blood sampling			X[h]	X[h]	X[h]	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	

Visit Identifier[a]	Screen		Periods 123[b] (45 day washout in between drug administration)																
		Day -1	Day 1						Day 2		Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 11	Day 15	Day 21	Follow-up*
Hours Post Dose			**-1**	**-0.5**	**-0.25**	**0**	**1**	**8**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	**168**	**240**	**336**	**480**	
Serious and non-serious AE monitoring	X	X		X ---------- X ----------																
Prior and concomitant treatment(s)	X	X				X				→	→	→	→	→	→	→	→	→	X	
CRU discharge[i]										X										

Abbreviations: → = ongoing/continuous event; AE = adverse event(s); BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; HCVAb = hepatitis C antibody; HepBcAb = hepatitis B core antibody; HepBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; PK = pharmacokinetic; PSA = Prostate Specific Antigen.

a. Day relative to start of study treatment (Day 1).
b. Part 2 only.
c. For inclusion into the study, one sample resulting in a serum testosterone of <250 ng/dL must be confirmed.
d. Performed at the discretion of the investigator.
e. A full exam will be performed at Day -1 for Period 1 if deferred from previous screening visit; A limited physical exam to be undertaken at Day -1 if full exam already performed at previous screening visit. A full physical exam will be performed in Period 2, Day -1.
f. A full physical exam will be performed at Part 2 Period 3 Day 21 only or upon study discontinuation.
g. The investigator must assess and document in the source if the subject is biologically capable of having children and if the subject continues to be or has become sexually active. If yes, their method of contraception and confirmation of its consistent and correct use must also be documented in the source documents.
h. Four pre-dose samples will be collected at -1, -0.5, -0.25, and 0 hours to determine endogenous levels of baseline testosterone. Samples should be collected between 7 and 8 am if dosing occurs for example at 8 am (recommended). A window of no more than 2 hours is allowed (ie, 6-8 am).
i. Subjects may remain at the CRU for longer period of time at the discretion of the investigator.

* A follow-up contact with the subject must be scheduled at the end of the AE/SAE active collection period. See the Follow-up section (Section 6.3).

1. INTRODUCTION

The current presentation of testosterone cypionate solution for injection (200 ng/mL) is highly concentrated (supersaturation) with respect to the active API and therefore makes the product susceptible to crystallization when exposed to lower temperatures than recommended on the approved label [20°C to 25°C (68°F to 77°F)]. Currently the product USPI1 includes "Warming and shaking the vial should re-dissolve any crystals that may have formed during storage at temperatures lower than recommended". To avoid crystallization and maintain true solution properties, the 200 mg/mL formulation is being modified to improve the solubility of the active ingredient in the vehicle, via an increase in the concentration of benzyl benzoate from 20% to 30% and a commensurate reduction in cottonseed oil from 560 mg to 470 mg to maintain mass balance. The current study will be assessing the BE and tolerability between the currently approved formulation and the reformulated presentation of testosterone cypionate solution for injection.

1.1. Mechanism of Action/Indication

Testosterone cypionate solution for injection is indicated for replacement therapy in males in conditions associated with symptoms of deficiency or absence of endogenous testosterone.[1]

- Primary hypogonadism (congenital or acquired)-testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome; or orchidectomy.

- Hypogonadotropic hypogonadism (congenital or acquired)-idiopathic gonadotropin or Luteinizing Hormone Releasing Hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation.

1.2. Background

Endogenous androgens are responsible for normal growth and development of the male sex organs and for maintenance of secondary sex characteristics.[1] These effects include growth and maturation of the prostate, seminal vesicles, penis, and scrotum, development of male hair distribution, such as beard, pubic, chest, and axillary hair, laryngeal enlargement, vocal cord thickening, and alterations in body musculature and fat distribution. Drugs in this class also cause retention of nitrogen, sodium, potassium, and phosphorous, and decreased urinary excretion of calcium. Androgens have been reported to increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein.

During exogenous administration of androgens, endogenous testosterone release is inhibited through feedback inhibition of pituitary luteinizing hormone (LH). At large doses of exogenous androgens, spermatogenesis may also be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH). There is a lack of substantial evidence that androgens are effective in fractures, surgery, convalescence, and functional uterine bleeding.

Testosterone esters are less polar than free testosterone. Testosterone esters in oil when injected intramuscularly are absorbed slowly from the lipid phase; thus, testosterone cypionate solution for injection can be given at intervals of 2 to 4 weeks.

Following IM administration in an oily vehicle, testosterone ester is slowly absorbed into the general circulation and then rapidly hydrolysed in plasma to testosterone. In a randomized cross-over study of 6 healthy males, the PK of a single injection of 200 mg testosterone cypionate was compared to that of a single injection of 194 mg testosterone enanthate. Mean serum testosterone concentrations increased to 3 times the basal levels at 24 hours and declined gradually to basal levels by Day 10. Testosterone in plasma is 98% bound to a specific testosterone-estradiol binding globulin, and about 2% is free. About 90% of a dose of testosterone is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver. Testosterone is metabolized to various 17-keto steroids through 2 different pathways. The half-life of testosterone cypionate when injected intramuscularly is approximately 8 days. Testosterone cypionate for IM injection is currently approved for testosterone replacement therapy in hypogonadal men.

Prolonged use of high doses of androgens has been associated with the development of hepatic adenomas, hepatocellular carcinoma, and peliosis hepatis, all potentially life-threatening complications. Long-term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiologic studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular events (MACE). Some studies, but not all, have reported an increased risk of MACE in association with use of testosterone replacement therapy in men. Patients should be informed of this possible risk when deciding whether to use or to continue to use DEPO-Testosterone (testosterone cypionate). Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids. Edema, with or without congestive heart failure, may be a serious complication in patients with pre-existing cardiac, renal or hepatic disease. Gynecomastia may develop and occasionally persist in patients being treated for hypogonadism.

Additional information for this compound may be found in the single reference safety document, which for this study is the Depo-Testosterone USPI.[1]

1.3. Rationale

1.3.1. Study Rationale

The current study will be assessing the BE between the current formulation (Reference formulation) and the reformulated presentation of testosterone cypionate injection (Test formulation) at a single 200 mg IM dose administered deep in the gluteal muscle. Since endogenous testosterone can interfere with the interpretation of systemic testosterone levels, the study will be conducted in hypogonadal males defined as subjects having serum testosterone levels below 2.5 ng/mL (250 ng/dL). Overall, the study design incorporates

2 parts. As the variability associated with the PK of the reformulated presentation of testosterone cypionate solution for injection is unknown, Part 1 will assess the variability associated with exposures after administration of both the current formulation and reformulated presentation of testosterone cypionate solution for injection. Part 2 will evaluate the BE between both test and reference treatments.

1.3.2. Dose Rationale

Testosterone cypionate solution for intramuscular injection is currently approved for testosterone replacement therapy in hypogonadal men. Testosterone cypionate solution for injection is available as 100 mg/mL strength (in 10 mL vials) and in 200 mg/mL strength (in 1 and 10 mL vials). The suggested dosage for testosterone cypionate solution for injection varies depending on the age, sex, and diagnosis of the individual patient. Dosage is adjusted according to the patient's response and the appearance of adverse reactions. For testosterone replacement therapy in the hypogonadal male, it is recommended that 50-400 mg should be administered every 2 to 4 weeks (per the USPI).[1] A 200 mg dose is selected for this study as the recommended dose in the drug label for hypogonadal males is 200 mg administered IM every 2 weeks (USPI).[1]

2. STUDY OBJECTIVES AND ENDPOINTS

Part 1	
Primary Objective:	**Primary Endpoints:**
• To estimate the exposure variability of the test and reference formulations of testosterone cypionate solution for injection (200 mg) given intramuscularly as a single dose.	• AUC_{last}, AUC_{inf} and C_{max} of total testosterone (baseline corrected).
CCI	

	• CCI [redacted]
Part 2	
Primary Objective:	**Primary Endpoints:**
• To evaluate the BE of the new formulation (testosterone cypionate solution for injection; 200 mg) relative to the currently marketed formulation (testosterone cypionate solution for injection; 200 mg) administered intramuscularly as a single dose.	• AUC_{last}, AUC_{inf} (if data permit), and C_{max} of total testosterone (baseline corrected).
CCI [redacted]	[redacted]

3. STUDY DESIGN

3.1. Study Overview

This is an open-label, randomized, 2-treatment, single-dose, cross-over study, 2-part design to evaluate the BE and tolerability of testosterone cypionate solution for injection (IM) administration in healthy hypogonadal male subjects (ages of 18 to 65 years). In Part 1, approximately 12 subjects will be enrolled in the study to ensure 10 evaluable subjects are to be randomized according to a computer-generated randomization schedule to receive the following 2 treatments below in random order.

Treatment A: A single testosterone cypionate solution for injection (new formulation) 200 mg dose administered IM deep in the gluteal muscle (Test).

Treatment B: A single testosterone cypionate solution for injection (currently marketed formulation) 200 mg dose administered IM deep in the gluteal muscle (Reference).

In Part 2, the observed variability associated with C_{max} and AUC as well as the point estimates obtained from Part 1, were used to estimate the sample size needed to attain bioequivalence (BE) in Part 2. In Part 2, it is anticipated that approximately 60 subjects will be enrolled to ensure 57 evaluable subjects. Subjects will be randomized according to a computer-generated randomization schedule to receive the 2 treatments (eg, same as listed in Part 1) in a random order.

As results from Part 1 demonstrated within-subject variability ≥30% (eg, highly variable drug) with respect to baseline corrected testosterone PK parameters, the study design and methodology for data analysis of Part 2 has been modified to a partial replicate design.

Table 2. Study Schematics

Part 1 (12 subjects[a])			
Sequence	**Period 1**	**Washout Period**	**Period 2**
1 (6 subjects)	Test treatment	At least 45 days	Reference treatment
2 (6 subjects)	Reference treatment		Test treatment

Part 2 (60 subjects[b])					
Sequence	**Period 1**	**Washout Period**	**Period 2**	**Washout Period**	**Period 3**
1 (20 subjects)	Test treatment	At least 45 days	Reference treatment	At least 45 days	Reference treatment
2 (20 subjects)	Reference treatment		Test treatment		Reference treatment
3 (20 subjects)	Reference treatment		Reference treatment		Test treatment

a. In Part 1, approximately 12 subjects will be enrolled to ensure 10 evaluable subjects.
b. In Part 2, approximately 60 subjects will be enrolled to ensure 57 evaluable subjects.

Screening evaluation will occur within 28 days prior to the first dose of study medication. Day -1 is defined as the day prior to first day of dosing (Day 1) for each study treatment. Subjects will be admitted to the Clinical Research Unit (CRU) on Day -1 and will remain at the CRU on Days 1-2 following administration of study medication. Subjects will be asked to return to the clinic for each subsequent PK sampling through Day 21. Subjects may remain at the CRU for a longer period of time at the discretion of the investigator. The baseline endogenous testosterone level will be the mean of four (4) pre-dose PK samples collected at -1.0, -0.5, -0.25 and 0 hours so that an average baseline correction of endogenous total testosterone levels can be calculated. These 4 pre-dose samples should be collected between the hours of 07:00 and 08:00 AM on the day of study drug administration, if dosing occurs for example at 8 am (recommended). A window of no more than 2 hours is allowed (ie, 6-8 am).

On Day 1, subjects will receive a single IM dose of either Test or Reference treatment according to randomization code. There will be at least a 45-day washout period between administration of each study medication in both Parts 1 and 2.

Blood samples (6 mL each) will be collected prior to dosing (-1.0, -0.5, -0.25, and 0) and at 1, 8, 24, 36, 48, 72, 96, 120, 144, 168, 240, 336, and 480 hours post-dose for analysis of total testosterone (free and protein bound) and its metabolite, dihydrotestosterone (DHT).

Tolerability and safety will be assessed for all treatments by monitoring adverse events (AE) s.

For Part 1, each subject will participate in the study with the duration of approximately 19 weeks from the time the subject signs the informed consent form through the final contact/follow-up contact. This includes a screening phase up to 4 weeks (28 days), ~10 weeks for dosing assuming, 45 days between treatments and up to 5 weeks for follow-up contact.

For Part 2, each subject will participate in the study with the duration of approximately 25 weeks from the time the subject signs the informed consent form through the final contact/follow-up contact. This includes a screening phase up to 4 weeks (28 days), assuming ~16 weeks for dosing, 45 days between treatments and up to 5 weeks for follow-up contact.

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment in the study:

1. Hypogonadal male subjects who, at the time of screening, are otherwise healthy and between the ages of 18 and 65 years, inclusive. Healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure (BP) and pulse rate measurement, 12-lead electrocardiogram (ECG), or clinical laboratory tests.

   Hypogonadism is defined as serum testosterone level below 2.5 ng/mL (250 ng/dL).

2. Body mass index (BMI) of 17.5 to 35 kg/m2; and a total body weight >50 kg (110 lb).

3. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

4. Subjects who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

2. Subjects who are currently being treated for hypogonadism. This is defined as patients who have received a testosterone injectable product within the past 3 months or have used a transdermal or gel product within the past 2 weeks.

3. A positive urine drug test.

4. History of regular alcohol consumption exceeding 14 drinks/week (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) within 6 months before screening.

5. Treatment with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of investigational product (whichever is longer).

6. Screening supine systolic BP 90-150 mm Hg (inclusive) or diastolic BP 50-95 mm Hg (inclusive), following at least 5 minutes of supine rest. If BP is ≥150 mm Hg (systolic) or ≥95 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the subject's eligibility.

7. Screening supine 12-lead ECG demonstrating a corrected QT (QTc) interval >450 msec or a QRS interval >120 msec. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine the subject's eligibility.

8. Subjects with ANY of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level ≥3 × upper limit of normal (ULN);

    - Total bilirubin level ≥1.5 × ULN; subject with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

9. Fertile male subjects who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol [Contraception (Section 4.3.4)] for the duration of the study and for at least 45 days after the last dose of investigational product.

10. Use of prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of investigational product. As an exception, acetaminophen/paracetamol may be used at doses of ≤1 g/day. Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

11. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 56 days prior to dosing.

12. History of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C; positive testing for HIV, hepatitis B surface antigen (HepBsAg), hepatitis B core antibody (HepBcAb), or hepatitis C antibody (HCVAb).

13. History of sensitivity to heparin or heparin-induced thrombocytopenia.

14. Unwilling or unable to comply with the criteria in the Lifestyle Requirements section of this protocol.

15. Subjects who are investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

16. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

17. Subjects with carcinoma of the breast.

18. Subjects with known or suspected carcinoma of the prostate gland.

19. Subjects who are hypersensitive to testosterone cypionate or its inactive ingredients.

4.3. Lifestyle Requirements

The following guidelines are provided:

4.3.1. Meals and Dietary Restrictions

- Subjects must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the predose PK sample. Water is permitted until 1 hour prior to investigational product administration.
- Water may be consumed without restriction beginning 1 hour after dosing.
- Non-caffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices, see below) may be consumed with meals and the evening snack.
- Lunch will be provided approximately 4 hours after dosing.
- Dinner will be provided approximately 9 to 10 hours after dosing.
- An evening snack may be permitted.
- While confined, the total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per subject should not exceed approximately 3200 kcal.

4.3.2. Alcohol, Caffeine, and Tobacco

- Subjects will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample of each study period. Subjects may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.
- Subjects will abstain from caffeine-containing products for 24 hours prior to the start of dosing until collection of the final PK sample of each study period.
- Subjects will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to dosing and during confinement in the CRU.

4.3.3. Activity

Subjects will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

4.3.4. Contraception

All fertile male subjects, who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 45 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his or partner(s) from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

- Correctly placed copper-containing intrauterine device (IUD).
- Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.
- Male sterilization with absence of sperm in the postvasectomy ejaculate.
- Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 45 days after the last dose of testosterone cypionate.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study supporting documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational products are:

- Testosterone Cypionate Solution for Injection 200 mg/mL (Test);
- Testosterone Cypionate Solution for Injection 200 mg/mL (Reference).

5.1. Allocation to Treatment

The investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

The investigator will assign subject numbers to the subjects as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the subject will receive the study treatment regimen assigned to the corresponding randomization number.

5.2. Subject Compliance

Investigational product will be administered under the supervision of investigator site personnel.

For Part 1, Subjects will be admitted to the CRU on Day -1 of Periods 1 and 2, will remain at the CRU on Days 1-2 during those periods and will be supervised by the site staff.

For Part 2, Subjects will be admitted to the CRU on Day -1 of Periods 1, 2 and 3, will remain at the CRU on Days 1-2 during those periods and will be supervised by the site staff.

Subjects may remain at the CRU for a longer period of time at the discretion of the investigator.

Treatment compliance will be ensured by the following procedures:

- For each subject, all doses of the study drug will be administered per the timing described in the protocol Schedule of Activities and by the appropriately designated study staff at the CRU.

- Study drug administration will be recorded in the source documents and entered in the appropriate section of the case report form (CRF). Any problems with the injection will be recorded in the source documents and in the CRFs.

5.3. Investigational Product Supplies

5.3.1. Dosage Form and Packaging

Testosterone cypionate solution for injection 200 mg/mL sterile vials will be supplied to the CRU by Pfizer as packaged Single Dose Vial (SDV) and labeled according to local regulatory requirements. Each SDV and the outer carton will contain a single panel label and will be provided in Open-Label fashion. The vials will be provided to the site for dispensing by the pharmacy.

Pivotal BE retain vials will be supplied to the CRU in individual labeled containers (in sufficient number to allow unopened containers to be kept as retains).

5.3.2. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the investigational product ready for administration or dispensing to the subject/caregiver by qualified staff. Dispensing is defined as the provision of investigational product, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, subject, or caregiver in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

See the Investigational Product (IP) Manual for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

5.4. Administration

Dosing will be administered on Day 1 of each Study Period by qualified medical personnel. The time of each drug administration will be recorded to the nearest minute.

The dose of testosterone cypionate (eg, investigational product) to be administered in this study is 200 mg in 1 mL solution. Each subject will receive either 200 mg of testosterone cypionate (Test) or 200 mg of testosterone cypionate (Reference) as a single IM dose in a particular treatment period. The investigation product will be administered according to the IP Manual. Each dose of study drug will be administered as an IM injection deep in the gluteal muscle in the same region for both periods.

In order to standardize the conditions on PK sampling days, all subjects will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

5.5. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

Any storage conditions stated in the single reference safety document (SRSD) will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product-label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

5.6. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

All pivotal BE retained vials may be sent to an off-site location for long-term storage after study closeout. Sample retention is the responsibility of the entity performing the BE study.

5.6.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.7. Concomitant Treatments

Subjects will abstain from all concomitant treatments, except for the treatment of AEs. Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of investigational product will be documented as a prior treatment. Treatments taken after the first dose of investigational product will be documented as concomitant treatments.

6. STUDY PROCEDURES

6.1. Screening

Refer to Schedule of Activities for the study procedures to be completed at the screening visit.

Subjects will be screened **within 28 days** prior to administration of the investigational product to confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in the Subject Information and Consent section (Section 12.3).

To prepare for study participation, subjects will be instructed on the Lifestyle Requirements (Section 4.3) and Concomitant Treatments (Section 5.7) of this protocol.

6.2. Study Period

Refer to Schedule of Activities for the study procedures to be completed. For the study period described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible.

- ECGs: obtain prior to vital sign measurements and as close as possible to the scheduled time, but prior to blood specimen collection;
- BP/pulse rate: obtain as close as possible to the scheduled time, but prior to blood specimen collection;
- PK blood specimens: obtain at the scheduled time;
- Other procedures: obtain all other procedures as close as possible to the scheduled time, but may be obtained before or after blood specimen collection.

When an intravenous (IV) catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate and BP) should be collected prior to the insertion of the catheter.

- There will be an interval of at least 45 days between study periods (ie, administration of subsequent doses of investigational product will not occur until at least 45 days after the previous dose of investigational product). All study periods will be conducted identically to that described above.

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the subject may be asked to remain in the CRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up.

If the subject is unable or unwilling to remain in the CRU and/or when outpatient follow-up is deemed appropriate, the Pfizer medical monitor (or designated representative) should be so notified, and the investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.3. Follow-up

6.3.1. Follow-up Contact

Follow-up contact will be completed at least 28 calendar days and up to 35 calendar days after the last administration of the investigational product to capture any potential adverse events (see the Time Period for Collecting AE/SAE Information section) and to confirm appropriate contraception usage (see the Contraception section). Contact with the subject may be done via a phone call.

6.4. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to AEs section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given investigator site. The early termination visit applies only to subjects who are randomized and then are prematurely withdrawn from the study.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The investigator or site staff should attempt to contact the subject twice. After 2 attempts, CRU staff may send a registered letter. If no response is received from the subject, the subject will be considered lost to follow-up. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

Lost to follow-up is defined as:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up 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 lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

It may be appropriate for the subject to return to the clinic for final safety assessments to be scheduled as early as practically feasible following the decision to withdraw from the study. Subjects should be questioned regarding their reason for withdrawal. At the early-withdrawal visit, every effort must be made to complete the following assessments:

- Full physical examination, if there is a new or open AE or clinically significant abnormal physical finding from the last visit;
- Supine BP and pulse rate measurements;
- 12-Lead ECG measurement;
- Blood and urine specimens for safety laboratory;
- Blood sample for PK analysis.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the subject's safety was preserved.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Withdrawal of consent is defined as:

Subjects who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Subjects who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

7. ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Safety

7.1.1. Laboratory Tests

The following safety laboratory tests will be performed at times defined in the Schedule of Activities/STUDY PROCEDURES section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 3. Safety Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/urea and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	Urine drug screening HIV HepBcAb HepBsAg HCVAb PSA
	Additional Tests (Needed for Hy's Law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels		

Abbreviations: abs = absolute; ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; CO_2 = carbon dioxide; GGT = gamma-glutamyl transpeptidase; HepBcAb = hepatitis B core antibody; HepBsAg = hepatitis B surface antigen; HCVAb = hepatitis C antibody; HIV = human immunodeficiency virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; PSA=Prostate Specific Antigen; qual = qualitative; RBC = red blood cell(s); WBC = white blood cell(s).

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.

- The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines.

- Subjects may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for subjects to receive investigational product.

7.1.2. Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems. The limited or abbreviated physical examination will be focused on general appearance, the respiratory and cardiovascular systems, and subject-reported symptoms.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

7.1.3. Blood Pressure (BP) and Pulse Rate

BP and pulse rate will be measured at times specified in the Schedule of Activities/STUDY PROCEDURES section of this protocol. Additional collection times, or changes to collection times, of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Supine BP will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Subjects should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

7.1.4. Electrocardiogram (ECG)

12-Lead ECGs should be collected at times specified in the Schedule of Activities/STUDY PROCEDURES section of this protocol.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position.

To ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements from the current period. If the QTc interval is increased by ≥45 msec from the baseline, or an absolute QTc value is ≥500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2 to 4 minutes apart, to confirm the original measurement. If either of the QTc values from these repeated ECGs remains above the threshold value (ie, is ≥45 msec from the baseline, or is ≥500 msec), then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If QTc values remain ≥500 msec (or ≥45 msec from the baseline) for greater than 4 hours (or sooner, at the discretion of the investigator), or QTc intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than 500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

7.2. Pharmacokinetics (PK)

7.2.1. Serum for Analysis of Testosterone and Dihydrotestosterone

During all study periods, blood samples (6 mL) to provide approximately 2.5 mL serum for PK analysis will be collected into appropriately labeled tubes at times specified in the Schedule of Activities section of the protocol.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF). It is important to note, that for baseline testosterone samples (4 pre-dose) it is recommended to obtain samples from 7-8 am, if dosing occurs for example at 8 am (recommended). A window of no more than 2 hours is allowed (ie, 6-8 am).

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures (SOPs).

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

As part of understanding the PK of the investigational product, samples may be used for metabolite identification and/or evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the clinical study report (CSR).

7.3. Blood Volume

The total blood sampling volume for individual subjects in Part 1 of this study is approximately 204 mL. The total blood sampling volume for individual subjects in Part 1 of this study is approximately 306 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs;

(2) non-serious AEs; and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become

immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject or legally acceptable representative. In addition, each study subject or legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal Section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

  Or that is considered to be:

  - An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are “susceptible” to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels.

Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.2. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.2.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

- An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products);

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.2.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.2.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.3. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.3.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

CCI

[redacted]

9.2. Efficacy Analysis

Efficacy analysis is not applicable to this study.

9.3. Pharmacokinetic Analysis

9.3.1. Derivation of Pharmacokinetic Parameters Prior to Analysis

PK parameters will be derived from the concentration-time profiles as shown in Table 4.

Table 4. Derivation of Pharmacokinetic Parameters

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear trapezoidal method
AUC_{inf}	Area under the plasma concentration-time profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
C_{max}	Maximum plasma concentration	Observed directly from data
CCI	[redacted]	[redacted]
$t_{½}$	Terminal elimination half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression

* If data permit.

9.3.2. Analysis Populations

The PK concentration population is defined as all subjects randomized and treated who have at least 1 concentration in at least 1 treatment period.

The PK parameter analysis population is defined as all subjects randomized and treated who have at least 1 of the PK parameters of primary interest in at least 1 treatment period.

9.3.3. Statistical Analyses of Pharmacokinetic Parameters

For each Part separately, natural log transformed AUC_{last}, AUC_{inf} (if data permit) and C_{max} of total testosterone (baseline corrected [mean of the 4 predose measurements] and uncorrected) will be analyzed separately using a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (Test – Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios.

Bioequivalence of the 2 treatments will be assessed in Part 2 and concluded if the 90% confidence intervals for the ratio of adjusted geometric means for AUC_{inf}, AUC_{last}, and C_{max} fall wholly within (80%, 125%). However, the bounds of the acceptance interval may be widened based on scaled bioequivalence methodology, which will be detailed in the Statistical Analysis Plan.

For each Part separately, the PK parameters for total testosterone (baseline corrected and uncorrected) of AUC_{inf}, AUC_{last}, percent of AUC_{inf} (if data permit) obtained by forward CCI [redacted] C_{max}, CCI [redacted] and terminal elimination half-life ($t_{½}$) (if data permit) will be summarized descriptively by analyte and treatment. The PK parameters for DHT of C_{max}, CCI [redacted] AUC_{inf}, AUC_{last}, (if data permits), and $t_{½}$ (if data permits) will also be summarized descriptively by analyte and treatment. For AUC_{inf}, AUC_{last} and C_{max}, individual subject parameters will be plotted by analyte and treatment. Concentrations will be listed by analyte and summarized descriptively by PK sampling time and treatment. Individual subject, mean and median profiles of the concentration-time data will be plotted by analyte against treatment (both linear and semi-log scales). For summary statistics and summary (mean and median) plots by sampling time, the nominal PK sampling time will be used. For individual subject plots by time, the actual PK sampling time will be used.

CCI [redacted]

CCI [redacted]

9.5. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/pharmacodynamic (PD) modeling, and/or supporting clinical development.

CCI [redacted]

Based on the results from Part 1, when the bioequivalence estimation was performed without the baseline correction, test formulation (Treatment A) was found to be bioequivalent to reference formulation (Treatment B) for AUC_{inf}, AUC_{last} and C_{max}. For all PK parameters the 90% CI for the ratio of the adjusted geometric mean fell within the 80-125% limits. However, when the data was analyzed with baseline testosterone correction, the 90% CI for the ratio for all the PK parameters was outside the 80%-125% limit. Importantly, the variability associated with AUC_{inf} was approximately 40%. The higher variability observed in these results as compared to the previous B5341001 study is the reason for the change in the original design of Part 2 from a 2-period crossover to a partial replicate design involving 3 periods.

Data Monitoring Committee

This study will not use a data monitoring committee (DMC).

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct for studies conducted at non-Pfizer investigator sites, to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

For studies conducted at non-Pfizer investigator sites, it is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include omitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked to ensure that only authorized study staffs have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s), or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent/assent document.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in the United States

Last subject last visit (LSLV) is defined as the date the investigator reviews the last subject's final safety data and determines that no further evaluation is required for the subject to complete the trial.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of testosterone cypionate solution for injection at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual patients have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publication by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publication by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

1. Depo-Testosterone (testosterone cypionate injection, USP) U.S. Prescribing Information. Pfizer, Inc. 2017.

Appendix 1. Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
Abs	absolute
AE(s)	adverse event(s)
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AUC	area under the curve
CCI [redacted]	[redacted]
AUC_{inf}	area under the plasma concentration-time profile from time 0 extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})
BE	bioequivalence
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CI	confidence interval
CK	creatine kinase
C_{last}	the last quantifiable concentration
C_{max}	maximum plasma concentration
CO_2	carbon dioxide (bicarbonate)
CRF	case report form
CRU	clinical research unit
CSA	clinical study agreement
CSR	clinical study report
CT	Clinical Trial
DCT	data collection tool
DEPO-Testosterone	Intramuscular depot formulation of testosterone cypionate
DHT	dihydrotestosterone
DILI	drug-induced liver injury
DMC	data monitoring committee
EC	ethics committee
ECG	electrocardiogram
EDP	exposure during pregnancy
EU	European Union
EudraCT	European Clinical Trials Database
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HCVAb	hepatitis C antibody
HepBcAb	hepatitis B core antibody

Abbreviation	Term
HepBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IM	intramusclar
IND	investigational new drug application
INR	international normalized ratio
IP manual	investigational product manual
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
LFT	liver function test
LH	luteinizing hormone
LHRH	Luteinizing Hormone Releasing Hormone
LSLV	last subject last visit
MACE	major adverse cardiovascular events
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
N/A	not applicable
PCD	primary completion date
PD	pharmacodynamic
PI	principal investigator
PK	pharmacokinetic(s)
PSA	Prostate Specific Antigen
PT	prothrombin time
QTc	corrected QT
qual	qualitative
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SDV	Single Dose Vial
SOP	standard operating procedure
SRSD	single reference safety document
STOD	Study Team On Demand
$t_{½}$	terminal elimination half-life
TBili	total bilirubin
THC	tetrahydrocannabinol
CCI	[redacted]
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
WBC	white blood cell