CLINICAL STUDY PROTOCOL

A Single-Blind, Single-Arm, Multiple-Dose Study Evaluating the Safety and Efficacy of Testosterone Cypionate Administered Subcutaneously via a Weekly Auto-Injector in Adult Males With Hypogonadism Through Week 24.

Drug substance	Testosterone Cypionate
Protocol Number	AMN-TRT-001
CRO Project Number	AS/CT/CN/ENE-26/002
Version	4
Date	07/Aug/2026
Phase of study	Phase 3
Test product	Testosterone Cypionate (50 mg, 75 mg and 100 mg) auto-injector for subcutaneous use (Amneal Pharmaceuticals LLC)
Dosage and mode of administration	Testosterone Cypionate (50 mg, 75 mg and 100 mg) will be administered subcutaneously once weekly

Study Sponsor
Amneal Pharmaceuticals LLC,
50 Horseblock Road,
Brookhaven, NY 11719,
Tel. No.: 001-631.952.0214
Fax: 001-631.656.1009
.

Confidentiality Statement

Information contained in this document is proprietary to Amneal Pharmaceuticals LLC. All information in this document, including unpublished data, exclusively belongs to Amneal Pharmaceuticals LLC and must be treated as confidential. The information in this Protocol shall be used solely for the purpose of review by the appropriate ethics committee or investigators and only for performing this study. Any disclosure or use of such information not authorized in writing by Amneal Pharmaceuticals LLC is strictly prohibited.

SPONSOR'S DECLARATION

On behalf of Amneal Pharmaceuticals LLC, I have read, understood, and approved this Protocol. We agree to comply with all requirements regarding the obligations of the Sponsor and all other pertinent requirements of the International Conference on Harmonization of technical requirements forregistration of pharmaceuticals for human use guideline for Good Clinical Practice ICH E6 (R3) GCP, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), in accordance with Declaration of Helsinki (Helsinki, Finland, 2024), Good Clinical Laboratory Practice (GCLP) and applicable national regulatory guidelines.

Sponsor's Representative	
Ms. Janie M. Gwinn, Ph.D Vice President Regulatory Affairs, Amneal Pharmaceuticals LLC. **Phone:** 001.631.310.7392 **Fax:** 001.646.351.0286 **Email:** Janie.Gwinn@amneal.com	**Signature:** **Date:**

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol titled "A Single-Blind, Single-Arm, Multiple-Dose Study Evaluating the Safety and Efficacy of Testosterone Cypionate Administered Subcutaneously via a Weekly Auto-Injector in Adult Males With Hypogonadism Through Week 24".

I agree to conduct the study in accordance with this protocol and to comply with all requirements regarding the obligations of investigators and all other pertinent requirements of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline for Good Clinical Practice ICH E6(R3), the Code of Federal Regulations on the Protection of Human Patients (45 CFR Part 46), in accordance with Declaration of Helsinki, principles on Good Laboratory Practice (GLP) and all applicable regulatory requirements to assess study risks and benefits.

I further agree to ensure that all associates assisting in the conduct of the study are informed regarding their obligations.

I will ensure that the rights, safety, and welfare of participants under my care are protected. I agree to ensure that the study drug is used in accordance with this final protocol.

I agree to comply with all relevant Standard Operating Procedures (SOPs) required for the conduct of this study and would document any significant deviations occurring during the study.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

CONTACT DETAILS AND FACILITIES

Sponsor's Contact **Ms. Janie M. Gwinn, Ph.D** Vice President Regulatory Affairs, Amneal Pharmaceuticals LLC. **Phone:** 001.631.310.7392 **Fax:** 001.646.351.0286 **Email:** Janie.Gwinn@amneal.com
Sponsor's Medical and Safety Expert Ronald Sanwo, M.D, MPH Pharmacovigilance Safety Physician, Amneal Pharmaceuticals LLC Tel. +1-877-835-5472 Fax: 631-983-2591 Email: drugsafety@amneal.com
Clinical laboratory Eurofins Central Laboratory LLC, 2430 New Holland Pike, D100, Lancaster. PA, USA, 17601.
Bioanalytical Facility Bioanalytical Unit, Avant Santé Research Center S.A. de C.V., Avenida Lázaro Cárdenas No. 500, Col Residencial San Agustín, San Pedro Garza García, N.L., México, C.P 66260. Tel.: +52 (81) 8248-2200 to 2210
Pharmacokinetics & Biostatistics facility Learn and Confirm Inc 750 Marcel-Laurin, Suite 235 St-Laurent, QC, H4M 2M4 Canada info@learnandconfirm.ca Phone and fax: 514 373-5346
Data Management CRO designated facility will perform data management activities.

Table of Contents

CONTACT DETAILS AND FACILITIES 4

Protocol Synopsis 10

1. Background Information 34

2. Study Objectives and Endpoints 40

3. Trial Design 43

3.1 Study Design 43

3.2 Study Visits and Procedures 46

3.2.1 Study Conduct 49

3.2.1.1 Screening Phase 49

3.2.1.2 Treatment Phase (Primary Evaluation Period: Through Week 24) 50

3.2.1.3 Continued Safety Follow-Up (Beyond Week 24) 60

3.2.1.4 End of Study Safety Follow-up (7-14 days After EOT) 66

3.3 Treatment Assignment 66

3.3.1 Participant Identification 67

3.4 Investigational Product Management 69

3.4.1 Study Medication (Investigational Product) Description 69

3.4.2 Study Medication Packaging and Label 69

3.4.3 Investigational Product Storage Conditions 70

3.4.4 Study Medication Accountability 71

3.4.5 Potentially Malfunctioned IMP 71

3.4.6 Handling of Retention Samples 72

4. Participant Selection and Withdrawal Criteria 73

4.1 Selection of Study Population 73

4.1.1 Inclusion Criteria 73

4.1.2 Exclusion Criteria 76
4.1.3 Enrollment Criteria for Treatment Initiation 79
4.2 Withdrawal/Discontinuation of Participants from Study Medication and/or the Study 80
4.2.1 Withdrawal of Participants from Follow-up/ Lost to follow-up: 81
4.2.2 Handling of Withdrawals 82
5. Treatment of Participants 84
5.1 Treatment 84
5.1.1 Study Drug and Administration Schedule 84
5.1.2 Study Restrictions 88
5.1.3 Treatment Compliance 89
5.1.4 Handling of Autoinjector Complaints 89
5.1.5 Overdose Management 89
6. Assessments of Efficacy and Related Parameters 90
6.1 Medical History 90
6.2 Demography 90
6.3 Assessment of Pharmacokinetic Parameters (C_{max}, $AUC_{0\text{-}168\ h}$, C_{trough}, and C_{avg}) 90
6.4 Meals 93
6.5 Blood Sample Processing 93
6.6 Bioanalytical Procedure and Sample Analysis 94
6.6.1 Sample Analysis 94
6.6.2 Procedure for Reanalysis 94
6.6.3 Recording and Reporting of Drug Concentrations 94
6.7 Pharmacokinetics Analysis 94
6.7.1 Data Entry 95
6.7.2 Pharmacokinetics Analysis 95

6.7.3 Pharmacokinetics Datasets 95

7. Assessments of Safety 97

7.1 Safety Monitoring 97

7.1.1 Vitals and Participant Well-being: 97

7.1.2 Ambulatory Blood Pressure Monitoring (ABPM) 98

7.1.3 Participant well-being questionnaire 98

7.2 Adverse Events 98

7.2.1 Definitions of Adverse Events 99

7.2.2 Assessment and Documentation of the Adverse Events 100

7.2.3 Abnormal Lab Results 101

7.2.4 Safety Monitoring Plan 102

7.2.5 Toxicity Grading Scale 102

A. Tables for Clinical Abnormalities 102

B. Tables for Laboratory Abnormalities 104

7.2.6 Reporting Adverse Events 108

7.2.7 Follow-Up of Participants Reporting Adverse Events 112

7.2.8 Concomitant Medications 112

7.2.9 Demographics, Physical Examination and Vital Signs 113

7.2.10 Electrocardiogram 113

7.2.11 Blood glucose monitoring and Management of anti-diabetic Medication in patients with Diabetes 113

7.3 Laboratory Analysis 114

8. Statistical Considerations 116

8.1 Study Disposition 116

8.2 Analysis Datasets 116

8.3 Data Analysis 117

8.3.1 Primary Efficacy Analysis: 117

8.3.2 Key Safety Endpoints: 117

8.3.3 Additional Secondary Efficacy Analysis 117

8.4 Interim and DSMB Anlayses 118

8.5 Missing Data 118

8.6 Demographic and Baseline Characteristics 118

8.7 Prior Medication and Concomitant Medication 118

8.8 Treatment Compliance 119

8.9 Confidence Interval (CI) 119

8.9.1 Safety Endpoints 119

8.10 Sample Size Calculations 121

8.11 Description of Subgroups to be Analyzed 122

8.11.1 Safety Analyses 122

8.11.1.1 Adverse Events 122

8.11.1.2 Other Safety Parameters 122

8.12 Deviations from the Planned Statistical Analysis 123

8.13 Data Quality Assurance 123

9. Data Handling and Record keeping 125

9.1 Case Report Forms/ Source Data Handling 125

9.2 Direct Access to Source Data/Documents 125

10. Quality Control and Quality Assurance 126

11. Ethical Considerations 127

11.1 Independent Ethics Committee or Institutional Review Board 127

11.2 Ethical Conduct of the Study 128

11.3 Participant Information and Consent 128

12. Investigator's Obligations 130

12.1 Confidentiality 130

12.2 Financial Disclosure and Obligations 130

12.3 Investigator Documentation 130

12.4 Study Conduct 131

12.5 Adverse Events and Study Report Requirements 131

12.6 Investigator's Final Report 131

12.7 Records Retention 131

13. Study Management 133

13.1 Monitoring 133

13.1.1 Monitoring of the Study 133

13.1.2 Inspection of Records 134

13.2 Management of Protocol Amendments and Deviations 134

13.2.1 Modification of the Protocol 134

13.2.2 Protocol Deviations 134

13.3 Study Termination 135

14. Financing and Insurance 136

15. Publication Policy 137

16. Reference List 138

17. Appendices 139

17.1 Appendix: Table of Study Assessment and Schedule of Events 139

Protocol Synopsis

Title	A Single-Blind, Single-Arm, Multiple-Dose Study Evaluating the Safety and Efficacy of Testosterone Cypionate Administered Subcutaneously via a Weekly Auto-Injector in Adult Males With Hypogonadism Through Week 24.
Protocol Number	AMN-TRT-001
Indication	Indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone
Study Phase	Phase 3
Study Centre(s)	Approximately 3-10 investigative sites in the US.
Rationale	Testosterone esters for intramuscular (IM) injection have been the standard of care for decades, but recently alternative modes of administration for testosterone and/or testosterone esters have been introduced including delivery via subcutaneous (SC) implant, transdermal delivery system (patch), hydroalcoholic gel for transdermal use, sustained-release buccal adhesive system and nasal gel. Testosterone replacement can be achieved in most patients through any of these delivery systems, though each regimen has its own set of risks, discomforts and inconvenience. Testosterone Cypionate is currently approved and marketed as an intramuscular product under the trade name Depo Testosterone (ANDA 085635). In contrast, the proposed Test Product is administered subcutaneously into the abdomen by the patient himself once weekly through use of the incorporated autoinjector. The principal potential benefit of this new approach is patient convenience.
Study Design	This is a Phase 3, Multi-Center, Single-Blind (with respect to dose strength), Single-Arm, Multiple-Dose Study Evaluating the Safety and Efficacy of Testosterone Cypionate Administered Subcutaneously via a Weekly Auto-Injector in Adult Males With Hypogonadism Through Week 24. Subjects may continue in a safety follow-up period beyond the 24-week. Participants / Patients will be required to have a documented diagnosis of hypogonadism to be eligible to enrol in this study. The study includes a Screening phase, a Treatment phase, and a continued safety follow-up beyond Week 24. Throughout the study, the principal investigator (PI) and an additional staff member (at the discretion of the PI) of the clinical site will remain unblinded to the testosterone cypionate dose for the participant safety monitoring and dose adjustment based on periodic serum

	total testosterone levels, as applicable. Study participants, and the clinical staff responsible for conducting study assessments will remain blinded (at the PI's discretion) to the assigned dose strength to minimize assessment, observation, and reporting bias.
Study Objectives	**Primary Objective:** To evaluate the safety and efficacy of testosterone cypionate auto-injector administered subcutaneously once each week via an auto-injector over a 24-week treatment period in adult males with hypogonadism. **Secondary Objectives:** • To evaluate the usability of the auto injector and associated Instructions for Use. • To characterize the response of total testosterone concentrations to dose adjustment. • To further characterize the safety and tolerability of testosterone cypionate administered subcutaneously once weekly via an auto injector beyond the 24 week primary evaluation period.
Screening Procedures	The participants will be screened for fasting serum total testosterone approximately 28 days prior to administration of first dose. Screening will be conducted only after obtaining informed consent, and will include the following: • Demographic data including date of birth, gender (Male), age, ethnicity, race, height, weight and body mass index (BMI). • Fasting Serum Testosterone test (total testosterone) will be performed between 07:30 AM - 10:00 AM on two separate days at least 72 hours during the screening period. One repeat total T concentration will be allowed if 1 of the 2 morning total T concentrations is ≥300 ng/dL. Hypogonadal male participants aged 18 to 75 years and having fasting morning (i.e., before 10 AM) serum total testosterone concentrations below 300 ng/dL, measured at least 72 hours apart within 28 days prior to first dose of study drug administration, within the BMI range of 18.5 to 39.9 kg/m^2 (inclusive) will be selected according to selection criteria and complete procedures outlined in 17.1 "Table of Study Assessment and Schedule of Events". Prior to the screening phase and before conducting comprehensive clinical laboratory assessments, all the participants may undergo at least one (1) qualifying serum testosterone concentration measurements to confirm hypogonadal status along with HbA1c and prostate serum antigen (PSA) evaluation. Participants meeting this preliminary study requirement, may then proceed to comprehensive clinical laboratory assessments as per the protocol.

	A participant may be rescreened once, at the discretion of the Investigator. Prior to performing any rescreening procedures, a new informed consent must be obtained from the participant. A new screening number will be assigned to the participant as per section 3.3.1.
Methodology	The pivotal phase 3 study has the following phases and visits: Clinical evaluations will be performed at: **Screening Phase (Approximately 4 weeks)** • **Visit 1: Screening** o Visit 1a: Testosterone qualification assessment o Visit 1b: Testosterone qualification assessment o Visit 1c: Additional qualification assessment (if required) **Treatment Phase (Primary Evaluation Period: Through Week 24)** • Visit 2: Week 1 (Day 1) – Initiation of treatment • Visit 3: Week 6 (Day 36) • Visit 4: Week 7 (Day 43) – Dose titration (if required) • Visit 5: Week 12 (Day 78) – (Evaluation of Primary Efficacy) • Visit 6: Week 13 (Day 85) – Dose titration (if required) • Visit 7: Week 18 (Day 120) • Visit 8: Week 19 (Day 127) – Dose titration (if required) • Visit 9: Week 24 (Day 162) – End of primary safety and efficacy evaluation **Continued Safety Follow-Up (Beyond Week 24)** • Visit 10: Week 25 (Day 169) – Dose titration (if required) • Visit 11: Week 30 (Day 204) • Visit 12: Week 31 (Day 211) – • Visit 13: Week 36 (Day 246) • Visit 14: Week 37 (Day 253) – Dose titration (if required) • Visit 15: Week 42 (Day 288) • Visit 16: Week 43 (Day 295) –

	• Visit 17: Week 52 (Day 358) – End of treatment or Study Completion for subjects who continue participation **Follow-Up** • Visit 18: Follow-up visit (7–14 days after last dose) **<u>Window period</u>** • All scheduled study activities should be performed on the designated study days. However, a visit window of ±2 days will be permitted for weekly dose administration and the corresponding study assessments from week 2 onward, except for the Week 12 dose administration, full PK sampling, and associated assessments. • The ±2-day visit window is not applicable to Week 12 dose administration for any subject. • **The Week 12 dose must be administered on the same weekday as the Week 1 dose administration.** • For the subset of 45 subjects participating in the intensive PK sampling schedule at Weeks 1 and 6, the ±2-day visit window is applicable only to Weeks 2, 3, 4, 5, and Weeks 7, 8, 9, 10, and 11. The Week 6 visit, including dose administration, full PK sampling, and all associated assessments, must be conducted on the scheduled study day without any visit window. • Whenever the ±2-day visit window is used for any weekly visit, subsequent weekly dose administrations must be rescheduled to the original Week 1 dosing weekday. The visit window does not permanently shift the dosing schedule.

Dose	Date of administration (Week day)
Week 1	Actual: 03/Aug/2026 (Monday)
Week 4	Schedule: 24/Aug/2026 (Monday)
Example 1, if window period of +2 days is used for week 4	
Week 4	Actual: 26/Aug/2026 (Wednesday)
Week 5	Schedule: 31/Aug/2026 (Monday) **and not 02/Sep/2026 (Wednesday)**
Example 2, if window period of -2 days is used for week 4	
Week 4	Actual: 22/Aug/2026 (Saturday)
Week 5	Schedule: 31/Aug/2026 (Monday) **and not 29/Aug/2026 (Saturday)**

- A visit window of ±2 days will also be permitted for C_{trough} sample required for dose titration at Week 6, 18, 24, and scheduled visits thereafter, and PK steady-state sample collection scheduled at Weeks 4, 5, 6 (except for the 45 subjects undergoing full PK sampling), 9, 10, and week 11. The visit window for PK sample collection and other scheduled study assessments will remain the same and will be referenced to the actual dosing time at the respective visit.

Screening Phase/Period

The screening period will be approximately 4 weeks in duration, depending on the washout period of the current therapy of each participant. All participants must have at least two qualifying serum testosterone concentrations values less than (<) 300 ng/dL obtained in the morning on two separate days measured at least 72 hours apart during the screening phase. During the screening phase, before conducting comprehensive clinical laboratory assessments, all the participants may undergo at least one (1) qualifying serum testosterone concentration measurements to confirm hypogonadal status along with HbA1c and prostate serum antigen (PSA) evaluation. Participants meeting this preliminary study requirement, may then proceed to comprehensive clinical laboratory assessments as per the protocol.

Treatment Phase/Period

All participants who meet the study eligibility criteria will be assigned study medication to receive Testosterone Cypionate 75 mg auto injector, once weekly.

Participant will come to the study site at the scheduled visits.

At week 1: The study medication will be administered by designated clinical study personnel to participants via subcutaneous route.
From week 2 to week 12: Participant will self-administer the study drug from week 2 to week 12. The study medication will be self-administered subcutaneously on the same day of each week and at approximately the same time (7:00 am ±2 hours) to ensure consistent dosing for Pharmacokinetic (PK) Analysis.
Dose Titration at Week 7: Dose adjustment will be made on day 1 of week 7 (visit 4) based upon day 1 of week 6 TT concentration (C_{trough} value).

Dose titration criteria will be as follows:

- Decrease dose by 25 mg if TT $C_{trough} \geq 650$ ng/dL
- Increase dose by 25 mg if TT C_{trough} <350 ng/dL
- Maintain dose strength if TT $C_{trough} \geq 350$ ng/dL and < 650 ng/dL

At Week 12 full PK (7- day) sampling for all participants: Blood samples for pharmacokinetic (PK) analysis of total testosterone (TT), dihydrotestosterone (DHT), dihydrotestosterone cypionate (DHTC), estradiol (E2), and testosterone cypionate (TC) will be obtained from all participants (please refer section "Blood PK Sampling Schedule") to measure at bioanalytical facility.
Pharmacokinetic parameters to characterize testosterone exposure over the 7-day dosing interval will be derived.

At Week 1 and Week 6 full PK (7- day) sampling for maximum of 45 participants: Blood samples for pharmacokinetic (PK) analysis of total testosterone (TT), dihydrotestosterone (DHT), dihydrotestosterone cypionate (DHTC), estradiol (E2), and testosterone cypionate (TC) will be obtained from 45 participants (please refer section "Blood PK Sampling Schedule") to measure at bioanalytical facility.

Pharmacokinetic parameters to characterize testosterone exposure over the 7-day dosing interval will be derived at week 1 and week 6.

Continued Safety Follow-Up
Completion of the Week 24 visit constitutes the primary safety and efficacy evaluation for the study. Subjects who complete this evaluation may continue to receive testosterone

	cypionate administered subcutaneously once weekly via an auto-injector, with ongoing safety assessment at scheduled visits. Subjects will remain on their individualized dose established during the primary evaluation period-week 24, with dose adjustments performed as clinically indicated at protocol-specified visits based on trough testosterone concentrations and the predefined dose titration criteria. The timing of dose assessments and potential adjustments is outlined in the Schedule of Assessments. Safety evaluations, including clinical laboratory testing, adverse event monitoring, and injection site assessments, will be conducted throughout the study at scheduled intervals. Final study evaluations will be performed 7 to 14 days after the last dose, including at the end of treatment or at early withdrawal. Additional follow-up may be conducted as needed to ensure resolution or stabilization of adverse events and any clinically significant abnormal findings.
Study Duration	The total duration of study participation for each subject will be up to 58 weeks, including a screening period of approximately 4 weeks, a 24-week primary treatment and evaluation period, continued treatment with ongoing safety assessment beyond Week 24, and a follow-up visit 7 to 14 days after the last dose.
Study Population	Male participants aged 18-75 years with the BMI range of 18.5 to 39.9 kg/m^2 with a diagnosis of Hypogonadism determined by having at least two qualifying total testosterone concentrations <300 ng/dL at the time of screening performed approximately within 28 days prior to first study drug administration.
Inclusion Criteria	1. Confirmation of Hypogonadism Before Initiation of Investigational Product: Ensure presence of at least one sign or symptom that may be related to low testosterone values and is/are consistent with hypogonadism which may include the following: •Decreased sexual desire •Decreased energy •Decreased facial or body hair •Loss of muscle mass and bone density •Erectile dysfunction •Low sperm count •Depressed mood

	•Lethargy •Sleep disturbances •Anemia •Changes in cholesterol levels •Mood changes • Irritability •Fatigue •Increase in body fat •Difficulty with concentration and memory •Decrease in endurance Prior to initiating investigational product (study drug) administration, the diagnosis of hypogonadism should be confirmed by ensuring that serum Total Testosterone concentrations have been measured in the morning on at least two separate days, at least 72 hours apart during screening period, and that these serum Total Testosterone concentrations should be as detailed below: 2. Participants with fasting morning total serum testosterone levels (measured on two separate days) < 300 ng/dL. 3. Qualifying total serum Testosterone (T) concentrations will be obtained on 2 separate occasions at least 72 hours apart during screening period. *One repeat total T concentration will be allowed if 1 of the 2 morning total T concentrations is ≥300 ng/dL. After retesting, if 2 of the 3 TT concentrations are <300 ng/dL, the participant will be eligible to participate in the study. The first total Testosterone (TT) concentration will be obtained after completion of washout from current Testosterone (T) therapy, if applicable.* 4. Prostate specific antigen (PSA) between 0-2.5 ng/mL for subjects ≤ 50 years of age and between 0-4 ng/mL for subjects > 50 years of age will be confirmed during screening. 5. Males (by birth) of 18 to 75 years of age with a documented diagnosis of hypogonadism having BMI range of 18.5 to 39.9 kg/m^2. 6. All participants will be required to agree to practice effective contraception throughout the duration of the study and for 30 days after receiving the last dose of testosterone. Acceptable methods of birth control included condom with spermicide, vasectomy, or monogamous relations with a female partner who are non-childbearing potential (post- menopausal, surgical or congenital sterility) or is

	of child-bearing potential and practiced a reliable method of contraception (hormonal contraception, double-barrier methods with spermicide, or intrauterine device). 7. Low-density lipoprotein cholesterol < 190 mg/dL. 8. Willing to give their written informed consent to participate in the study, able and willing to comply with all study procedures, including being available for all study Visits. 9. Adequate venous access to allow collection of a number of blood samples via a venous cannula 10. Participants without prior TRT use required to have haemoglobin (Hb) ⩽ 16 g/dL at baseline or should have Hb of ⩽17 g/dL for participants with TRT use within 30 days prior to screening. 11. Participants with diabetes mellitus may be enrolled, provided they have been on a stable dose and regimen of anti-diabetic medication(s) for at least 4 weeks prior to screening and have a HbA1c level ≤ 9.0%, or are considered adequately controlled at the discretion of the PI. 12. Participants with dyslipidaemia (hyperlipidaemia) may be enrolled, provided they have been on a stable dose and regimen of lipid-lowering medication(s) for at least 4 weeks prior to screening or are considered adequately controlled at the discretion of the PI. 13. Based on measurement of BP in the clinical site (using the cuff method), participants with hypertension (SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg) may be enrolled, provided they have been on a stable dose and regimen of antihypertensive medication(s) for at least 1 month prior to screening or are considered adequately controlled at the discretion of the PI. or Based on measurement of BP in the clinical site (using the cuff method), participants who are normotensive (SBP < 140 mm Hg and/or DBP < 90 mm Hg) and not receiving antihypertensive medication are also eligible for enrolment.
Exclusion Criteria	1. Individuals who have an allergic reaction or idiosyncratic reaction to cotton seed oil. 2. Current Opioid Use. 3. History of intolerance, allergy, or idiosyncratic reaction to testosterone products. 4. Body mass index (BMI) >40.0 kg/m^2. 5. Hematocrit ≥ 52% at the initial Screening Visit. 6. Individual history or current evidence of prostate cancer.

	7. Men with two (2) total testosterone levels below 100 ng/dL during the screening period. 8. Abnormal ECG considered clinically significant by investigator at Screening. Or History of long QT syndrome or unexplained sudden death in a first-degree relative (parent, sibling, or child). 9. Any malignancy, diagnosed or treated within 5 years of the date of Screening with the exception of non-melanoma carcinoma of the skin. 10. Presence of prostate nodule or induration upon digital rectal exam (DRE). 11. Obstructive uropathy of prostatic origin and of a severity that, in the opinion of the Investigator, contraindicated the use of T therapy and/or participants with lower urinary tract symptoms (LUTS), as indicated by an International Prostate Symptom Score (I-PSS) greater than 19. 12. Participants with New York Heart Association Class III or IV congestive heart failure prior to Visit 1. 13. Myocardial infarction, unstable angina leading to hospitalization, percutaneous coronary intervention, coronary artery bypass graft, uncontrolled cardiac arrhythmia, stroke, transient ischemia attack, carotid revascularization, endovascular procedure, or surgical intervention for peripheral vascular disease within 6 months prior to Visit 1 (Screening). 14. History or current treatment for thromboembolic disease or hypercoagulatory condition, or use of anti-thromboembolic medications. Use of low-dose aspirin (81 mg) will be permitted. 15. Participants using systemic adrenocorticotropic hormone or oral or depot corticosteroids. Inhaled corticosteroids for respiratory conditions are permissible. 16. Untreated sleep apnea. 17. Historical or current evidence of any clinically significant disease or disorder that, in the opinion of the Investigator, may have caused participation in the study to be detrimental to the participant or which may affect the results of the study. This includes cardiovascular, renal, hepatic, hematological, neuropsychological, endocrine, gastrointestinal, and pulmonary disease. Subjects with an endocrine disorder requiring treatment other than hypogonadism must be on a stable dose of replacement medication for at least 3 months prior to study entry. 18. Positive serology for human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (HCVAb) at the Screening Visit.

	19. History of drug or alcohol abuse within the past 2 years that in the opinion of the investigator could interfere with study participation and/or influence study efficacy and safety endpoints assessments. 20. A positive drug screen without documentation of a prescription and medical condition requiring treatment with the drug for which the screen was positive. Exception for tetrahydrocannabinol will be allowed in states where recreational use of marijuana is legal. 21. Clinically significant history tobacco or cigarette consumption as per the Investigator's discretion within 2 years of study period dosing. Light smokers (≤5 cigarettes per day) are allowed to take part in this study. 22. Participants with active suicidal ideation with method, intent, or plan (C-SSRS Categories 3, 4, or 5) during the last 6 months prior to screening. 23. Any history of a suicide attempt (C-SSRS Category 9) during the last 12 months prior to screening. 24. Any patient exhibiting new-onset or worsening depression, anxiety, or suicidal thoughts (Categories 1-2) during the last 6 months prior to screening. 25. Any skin condition that could confound injection site assessments (e.g., dermatographism, urticaria, or atopic dermatitis, tattoos, scarring, psoriasis, etc.) at the injection site. 26. Participants with history of and current deep venous thrombosis (DVT), pulmonary embolism (PE), or known thrombophilia. 27. Use of any drug that could interfere with measurement or assessment of serum androgen levels, including 5 alpha-reductase inhibitors, anabolic steroids, and drugs with anti-androgenic properties (e.g., spironolactone, cimetidine, flutamide, bicalutamide, and ketoconazole). These drugs must be stopped for at least 1 month prior to study entry (6 months in the case of dutasteride). Patients taking potent, short or long- acting opiate therapy on a daily basis are not eligible for the study. 28. Use of over-the-counter products (OTC) including natural health products (e.g., food supplements and herbal supplements such as saw palmetto or phytoestrogens) that may affect total T levels, within 7 days prior to study entry. 29. Participants who use clomiphene, enclomiphene or OTC androgenic steroid derivatives including investigation and drug products that may affect reproductive potential, or have been treated with such products in the past 6 months prior to screening (visit 1). 30. Exclude the following potential participants: a) Known history of polycythemia vera or secondary polycythemia, such as polycythemia due to untreated sleep apnea or severe chronic obstructive pulmonary disease (COPD). b) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than 3 times the upper limit of normal (ULN).

	c) Tattoo removal in the region of the study drug application within six months of screening (visit 1). d) Chronic kidney disease documented by an eGFR less than 30 mL/min calculated by CKD-EPI formula. e) History of use of an anti-estrogen treatment within 90 days prior to screening. f) Participants taking any high-potency opioids (e.g., oxycodone, hydrocodone, etc.) or glucocorticoids > 7.5 mg prednisone equivalents per day (e.g., hydrocortisone 30 mg, methylprednisolone 6 mg or dexamethasone 1.2 mg) within 1 week before the screening visit, except men who are taking these medications for a chronic condition and are anticipated to continue treatment. Inhaled corticosteroids for respiratory conditions are permissible. 31. Participants who are currently using 5-alpha reductase inhibitors (e.g., finasteride, dutasteride) 32. Administration of any other investigational compound within 1 month prior to Screening or 7 half-lives of the Testosterone (whichever was longer). 33. Within 12 months prior to Screening Visit 1, the participant has taken estrogen, gonadotropin-releasing hormone agonists, or growth hormone or anti-androgens. 34. Participants who have taken, long-acting opioid analgesics in last 1 month prior to study visit 2. 35. Participants who have taken other androgens (e.g., dehydroepiandrosterone [DHEA]), anabolic steroids, other sex hormones, or other substances/medications, including dietary supplements, known to affect the PK of study drug. a) Discontinuation of these substances/medications will be allowed at the initial Screening Visit provided that the half-life of the substance/medication allowed complete washout (minimum of 5 half-lives) during the washout section of the Screening Phase. Washout must be completed before the Qualification (Qual) Visit. b) DHEA will be required to be washed out for a minimum of 4 weeks. c) Participants who require the use of these substances /medications during the duration of the study will be excluded. 36. Concurrent treatment with medications that may impact the absorption, distribution, metabolism, or excretion of study drug or place the participant at risk for treatment with T. 37. Participant has a partner who is planning pregnancy during the course of the study. 38. Treatment with any other investigational drug within 30 days of study entry or > 5 half- lives (whichever is longer) and at any time during the study.

	39. History of noncompliance to medical regimens or potential unreliability in the opinion of the investigator. 40. Onset of gynecomastia within the previous 6 months. 41. Participants who will be considering or have scheduled any major surgical or dental procedure anticipated to be associated with significant blood loss (≥500 mL) during the study. 42. Participants who donated plasma or blood within 56 days of the Screening Visit or had a history of donation of more than 500 mL of blood or plasma within 3 months of Screening. Blood and plasma donation will be prohibited further during the duration of the study. 43. Unable to understand verbal or written English or any other language in which a certified translation of the informed consent is available. 44. If, for any reason, the investigator believes that the participant is not a viable candidate to receive the study drug.
Enrollment Criteria for Treatment Initiation period	Each participant in this study must meet all the following criteria at screening: • Adult male with a confirmed diagnosis of Hypogonadism containing consistent signs and symptoms of androgen deficiency and documented low total testosterone (TT) concentration (< 300 ng/dL). • Any of the following treatment regimens prior to the Screening Visit are acceptable: o Treatment-naïve (participants who have never received any form of testosterone replacement) o Currently treated with oral, buccal, or transdermal testosterone regimen (participants will undergo 2-week washout prior to visit 1). o Currently treated with a stable IM testosterone regimen (dose and interval) for a minimum of 3 consecutive doses (dose must be 50 mg to 400 mg administered at intervals no greater than every 4 weeks) (participants will undergo 5-week washout prior to visit 1); or o Completed washout of treatment prior to screening (i.e., 2-week washout for buccal or transdermal, or 5-week washout of IM testosterone or end of dosing interval for Testopel participants i.e. at least 12-weeks from the initiation, prior to visit 1). Participants who have completed washout of treatment prior to screening will follow the same procedures as participants who are treatment-naïve. • Qualifying Testosterone concentrations, obtained during screening/qualification visits as follows: o Treatment-naïve participants, or participants on current testosterone therapy who

<table>
<tr><td></td><td>have completed above defined minimum washout period must have 2 fasting morning TT concentrations <300 ng/dL during the screening period. Qualifying total Testosterone concentrations will be obtained between 07:30 AM - 10:00 AM on 2 separate occasions at least 72 hours apart during screening period.
o Participants who have 1 sample >300 ng/dL may have 1 retest for TT concentrations (Visit 1c) which must occur no less than 7 days after the previous test. After retesting, if 2 of the 3 TT concentrations are <300 ng/dL, the participant will be eligible to participate in the study.</td></tr>
<tr><td>Blood PK Sampling Schedule</td><td>Blood samples for PK analysis of TT, DHT, E2, dihydrotestosterone cypionate (DHTC) and Testosterone Cypionate will be obtained prior to dosing and at specified times up to 168 hours post dose at week 1, 6 and 12.

<u>Full PK (7- day) sampling will be performed for maximum of 45 participants at week 1, week 6 and all participants at week 12 and details are as follows</u>
<table>
<tr><td colspan="3"></td></tr>
<tr><td>Week</td><td>No. of Samples</td><td>Sampling schedule</td></tr>
<tr><td>1
(full PK)</td><td>10</td><td>0.00 (pre-dose sample), 0.50, 3.00, 6.00, 9.00, 12.00, 24.00, 48.00, 72.00, and 168.00* hours post-dose in plain vacutainers.
*:Corresponds to Day 1 of Week 2.</td></tr>
<tr><td>6
(full PK)</td><td>11</td><td>0.00 (pre-dose sample), 0.50, 3.00, 6.00, 9.00, 12.00, 24.00, 48.00, 72.00, 144.00, and 168.00* hours post-dose in plain vacutainers.
*:Corresponds to Day 1 of Week 7</td></tr>
<tr><td>12
(pivotal-full PK)</td><td>13</td><td>0.00 (pre-dose sample), 3.00, 6.00, 9.00, 12.00, 24.00, 36.00, 48.00, 72.00, 96.00, 120.00, 144.00, and 168.00* hours post-dose in plain vacutainers.
*: Corresponds to Day 1 of Week 13</td></tr>
<tr><td>4, 5, 9, 10 and 11
(steady-state)</td><td>5</td><td>Before dose administration</td></tr>
</table>
<table>
<tr><td colspan="3"><u>For all the participants full PK sampling will be performed at week 12 only and details are as follows.</u></td></tr>
<tr><td>Week</td><td>No. of Samples</td><td>Sampling schedule</td></tr>
</table></td></tr>
</table>

1, 4, 5, 6, 9, 10 and 11 (Pre-dose / steady-state)	7	Before dose administration
12 (full PK)	13	0.00 (pre-dose sample), 3.00, 6.00, 9.00, 12.00, 24.00, 36.00, 48.00, 72.00, 96.00, 120.00, 144.00, and 168.00* hours post-dose in plain vacutainers. *:Corresponds to Day 1 of Week 13

The acceptable window period of -15 (fifteen) minutes for 0.00 hours pre-dose samples.

Up to 24.00 h post-dose PK samples will be collected during housing period at study site with window period of ± 5 minutes, and rest all (up to 168.00 h) are collected as ambulatory PK blood samples (± 2 h)].

To ensure compliance with overnight fasting requirements, subjects may be housed at the clinical site when appropriate facilities are available.
For clinical sites that do not have the infrastructure to accommodate overnight stays, subjects may instead return to their homes and are instructed to maintain the required fasting conditions until they return to the site the following day for scheduled study procedures and /or PK sample blood sample collection. Upon arrival at the clinical site the next day, subjects will provide written confirmation that they adhered to the fasting requirements as instructed.
The 168-hour post-dose sample of week 1 dose corresponds to Day 8 of Week 1 (day 1 of week 2), the 168-hour post-dose sample of week 6 dose corresponds to Day 8 of Week 6 (day 1 of week 7), and the 168-hour post-dose sample of week 12 dose corresponds to Day 8 of Week 12 visit (day 1 of week 13) and it should be collected prior to dosing on that day.
C_{trough} samples: For dose titration, Trough TT blood samples will be obtained within 15 minutes before dose administration on Day 1 of week 6 (visit 3), week 12 (visit 5), week 18 (visit 7), week 24 (visit 9), and scheduled visits thereafter for all participants.

At week 1, since testosterone is an endogenous substance, the serum concentration of testosterone should be corrected for baseline endogenous levels by subtracting pre-dose baseline value (at 0.00 hours before dosing). Any negative value obtained from baseline correction should be designated as zero. For week 6 and week 12 PK profiles, baseline correction is not necessary.

	Note: The additional (maximum of 9) samples for serum TT will also be collected along with clinical laboratory assessments at selection (≤ 4 samples), for dose titration at week 18, 24, and scheduled visits thereafter, and these samples will be analysed for cross-validation only if the participants took at least 1 dose of study drug using LC/MS-MS method in bioanalytical facility, and results will be reported for information purpose.
Ambulatory Blood Pressure Monitoring	Ambulatory Blood Pressure Monitoring (ABPM) will be evaluated in each participant for a period of 24 hours (at least 0.5 hours prior to 24 hours post-dose) at the following: Baseline/pre-dose (week -1 to day 1*), day 1 of week 12 (visit 5), day 1 of week 24 (visit 9), and scheduled visits thereafter. If the subject misses ABPM evaluation on the scheduled day, the subject will be encouraged to perform on the next day to complete the 24-hr ABPM evaluation. *: could be during domicile or ambulatory but it should be completed before day 1/week 1 dose administration.
Bio Analytical Estimation of Analytes	Total testosterone (TT), dihydrotestosterone (DHT), dihydrotestosterone cypionate (DHTC), Estradiol (E2) and Testosterone Cypionate (TC) in serum at week 1*, 6* and 12 for full PK Samples, and week 4, week 5, week 6*, week 9, week 10 & week 11 for TT C_{trough} Measurement to evaluate Steady State. *: Full PK sampling at week 1 and week 6 is applicable only for 45 participants, and pre-dose sample and week 6 steady-state sample is applicable only for the rest of the participants. **Note:** The additional (maximum of 9) samples for serum TT will also be collected along with clinical laboratory assessments at selection (≤ 4 samples), for dose titration at week 18, 24, and scheduled visits thereafter, these samples will be analysed only if the participants took at least 1 dose of study drug using LC/MS-MS method in bioanalytical facility, and results will be reported for information purpose. Bioanalysis may be initiated after completion of Week 12 full PK profile of all the participants.
Endpoints / Outcome	**Primary Efficacy Endpoint** i. The primary efficacy endpoint in the study will be percentage of participants at week 12 with average serum Total Testosterone concentration ($C_{avg\ 0\text{-}168h}$) over the 7-day dosing interval (0-168 hours) to be within the defined range of 300 to 1100 ng/dL using full PK population data.

The primary endpoint will be satisfied if ≥75% of participants have serum Total Testosterone $C_{avg168h}$ within 300 to 1100 ng/dL at Week 12, with a lower bound of the 95% confidence interval (CI) at ≥65%.

The primary efficacy endpoint ($C_{avg\ 168h}$) is calculated from the AUC using the following formula;

$$C_{avg\ 168h} = AUC\ (0\text{-}168\ h) / 168$$

Key Safety Endpoints:

i. Percentage of participants with maximum (peak) serum Total Testosterone concentration (C_{max}) <1500 ng/dL. This endpoint will be satisfied if ≥85% of participants have serum Total Testosterone C_{max} <1500 ng/dL at Week 12 of treatment.

ii. Percentage of participants with serum Total Testosterone C_{max} between 1800 to 2500 ng/dL, (inclusive). This endpoint will be satisfied if <5% of participants have serum Total Testosterone C_{max} in the range of 1800 to 2500 ng/dL at Week 12 of treatment.

iii. Number of participants with serum Total Testosterone C_{max} >2500 ng/dL. This endpoint will be satisfied if no participants have serum Total Testosterone C_{max} >2500 ng/dL at Week 12 of treatment.

Additional Secondary Efficacy Analysis:

i. Number and percentage of participants with minimum serum concentration (C_{min}) of Total Testosterone <300 ng/dL at Week 12 of treatment.

ii. Serum Total Testosterone $C_{avg168h}$ within the defined range of 300 to 1100 ng/dL for the 75 mg autoinjector dose (that is, excluding participants on the 50 mg and 100 mg doses) at Week 12. Endpoint will be satisfied if ≥75% of participants with a lower limit of the 95% CI ≥65%, have serum Total Testosterone $C_{avg168h}$ within the defined range of 300 to 1100 ng/dL at Week 12 of treatment.

iii. Assuming sufficient numbers of participants receive the 100 mg dose of the autoinjector, the serum Total Testosterone C_{avg18h} at Week 12 will be calculated and presented with descriptive statistics.

iv. Assuming sufficient numbers of participants receive the 50 mg dose of autoinjector, the serum Total Testosterone $C_{avg168h}$ at Week 12 will be calculated and presented with descriptive statistics.

v. Single-dose area under the curve (AUC), C_{max}, time to maximum serum concentration (T_{max}) of Total Testosterone, and $C_{avg168h}$ for the 75 mg dose of

<table>
<tr><td></td><td>autoinjector at week 1 (with PK Population data).

Final details on the statistical analysis will be specified in the Statistical Analysis Plan.</td></tr>
<tr><td>Safety Endpoints</td><td>

Number (percent), severity, and relatability (Treatment/ Drug/ Device) of adverse events (AEs) and serious adverse events (SAEs)
Vital signs (Pulse rate, Axillary Body Temperature, Respiratory rate, Blood pressure)
ECG
Physical examinations, including Digital Rectal Exam (DRE)- if performed.
Laboratory examination assessment (except serology) from baseline to through the 24-week primary evaluation period and may continue at scheduled visits thereafter.
Use of anti-hypertensive medications (new initiation or dose adjustment) from baseline to through the 24-week primary evaluation period and may continue at scheduled visits thereafter.
Change from baseline in 24-hour mean systolic and diastolic blood pressure measured by continuous Ambulatory Blood Pressure Monitoring (ABPM) at Week 12, week 24, and scheduled visits thereafter, and over the course of the study.
Change from baseline in quality of life based on C-SSRS, HDRS, SIAQ, SF-36, Assessment of Essential Tasks Questionnaire at Week 24 and scheduled visits thereafter.

</td></tr>
<tr><td>Sample size</td><td>To estimate sample size for the phase 3 trial, Amneal developed and validated a Population PK model to simulate steady state concentrations of the Test Product at week 12. Assuming a minimum success rate of 90% for the primary endpoint based on $C_{avg\ 0\text{-}168}$ (Week 12 C_{avg} total testosterone concentration within the prespecified normal range of 300-1100 ng/dL), the study would need to finish with 60 subjects to obtain a lower bound of the 2-sided 95% CI that would be equal to or exceed 65%. Assuming a dropout rate of 25%, a minimum of 80 participants (for example 80-140 subjects) will need to be enrolled to ensure that at least 60-120 participants complete the study.
<table>
<tr><th colspan="4">Simulations to Estimate Sample Size With 75 mg As the Starting Dose</th></tr>
<tr><th rowspan="2">Sample Size (n)</th><th rowspan="2">Mean Passing Rate</th><th rowspan="2">95% LCI ($C_{avg0\text{-}168}$) (Mean)</th><th colspan="2">Week 12: Studies Meeting Criteria (%)</th></tr>
<tr><th>Based on $C_{avg0\text{-}168}$*</th><th>C_{max} > 2500 ng/dL (%)</th></tr>
</table>
</td></tr>
</table>

		($C_{avg0-168}$) (%)		**(%)**	
	Passing scores	≥ 75.0	≥ 65.0	> 80	> 80
	14 obs in silico	*92.9*	*66.1*	*N/A*	*N/A*
	14	85.7	58.0	36.0	100
	20	99.0	81.6	100	99.3
	40	98.9	89.3	100	99.3
	60	98.9	92.2	100	98.7
	80	98.9	93.6	100	98.3
	100	98.9	94.4	100	98.3
	120	98.9	95.1	100	98.0
	140	98.9	95.5	100	97.3
	160	98.9	95.8	100	97.0
	***Note:** Results based on 300 simulated clinical trials for all sample sizes, except for n=14 which was based on one *in silico* trial for the observed and 100 simulated clinical trials. N/A: Not Applicable				
Statistical Methods	The primary endpoint will be analyzed via analysis of covariance (ANCOVA) models. A two-sided, 95% confidence interval will need to equal or exceed 65% for the study's primary endpoints. **Population to be Analyzed:** Three participant populations are defined for analysis: • **Full Analysis Set (FAS):** This population consists of all participants who have received at least one dose of the study drug. • **PK population:** The PK population consists of all participants who receive study treatment and have at least one evaluable 168-hour PK profile of study treatment with calculable AUC, C_{max} and C_{avg} from 168-hour PK assessment at any scheduled full PK assessment visit (Week 1, Week 6, or Week 12). • **Full PK population:** The PK population consists of all participants in the study who have completed all 12 weeks of study treatment with calculable AUC, C_{max} and C_{avg} from 168-hour PK assessment at Week 12 with no significant protocol deviation. • **Safety population:** The safety population consists of all participants who took at least 1 dose of study drug.				

Safety Analysis:	All adverse events (AEs) will be reported, whether or not they are considered to be related to the treatment. The report of each AE should include the date of onset, description of AE, severity, relation to study medication, action taken, outcome, and date of resolution. The information will assist in evaluating the incidence and severity of adverse reactions. Adverse events (AEs) will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA®), as summarized by the treatment group, System organ class (SOC) and preferred term (PT). Summary tables of AEs comparing the intensity (severity) and relationship will be prepared by treatment group. All participants who are qualified for the treatment period of the study will be included in the comparative safety analysis. Concomitant medications will be classified according to the World Health Organization (WHO) Drug Dictionary and will be tabulated by treatment and presented as data listings.

List of Abbreviations

ABPM	:	Ambulatory Blood Pressure Monitoring
ADL	:	Activities of Daily Living
ADR	:	Adverse Drug Reaction
AE	:	Adverse Event
ALT	:	Alanine Transaminase
ALCOA-C	:	Attributable, Legible, Contemporaneous, Original, Accurate, and Complete
ANCOVA	:	Analysis of Covariance
AUC	:	Area Under the Curve
Avg	:	Average
BMI	:	Body Mass Index
Bpm	:	Beats Per Minute
BQL	:	Below Quantifiable Limit
CDISC	:	Clinical Data Interchange Standards Consortium
CD ROM	:	Compact Disc Read-Only Memory
CFR	:	Code of Federal Regulations
CI	:	Confidence Interval
Cmax	:	Maximum Concentration
C_{min}	:	Minimum Concentration
COPD	:	Chronic Obstructive Pulmonary Disease
eCRF	:	electronic Case Report Form
CRO	:	Contract / Clinical Research Organization
CSR	:	Clinical Study Report
CSCR	:	Central Serous Chorioretinopathy
C-SSRS	:	Columbia-Suicide Severity Rating Scale
CTCAE	:	Common Terminology Criteria for Adverse Events
C_{trough}	:	Concentration at Steady-State
CV	:	Coefficient of Variation
DBL	:	Database Lock

DBP	:	Diastolic Blood Pressure
DHT	:	Dihydrotestosterone
DHTC	:	Dihydrotestosterone Cypionate
DHEA	:	Dehydroepiandrosterone
DIC	:	Disseminated Intravascular Coagulation
DRE	:	Digital rectal Examination
DVT	:	Deep Vein Thrombosis
E2	:	Estradiol
ECG	:	Electrocardiogram
eCTD	:	Electronic Common Technical Documentation
EDC	:	Electronic Data Capture
EOS	:	End of Study
EOT	:	End of the Treatment
ET	:	Early Termination
FAS	:	Full Analysis Set
FDA	:	Food and Drug Administration
FPK	:	Full PK profile
GCP	:	Good Clinical Practice
GCLP	:	Good Clinical Laboratory Practice
Hb	:	Hemoglobin
HCV	:	Hepatitis C Virus
HIV	:	Human Immunodeficiency Virus
IEC	:	Institutional Ethics Committee
ICF	:	Informed Consent Form
ICH	:	International Conference on Harmonization
IM	:	Intramuscular
IMP/ IP	:	Investigational Medicinal Product / Investigational Product
I-PSS	:	International Prostate Symptom Score
IR	:	Insulin Resistance

IRB	:	Institutional Review Board
ISA	:	Injection site assessments
ISR	:	Incurred sample reanalysis
ISTR	:	Injection site reactions
IWRS	:	Interactive Web Response System
LAR	:	Legally Authorized Representative
LUTS	:	Lower Urinary Tract Symptoms
MACE	:	Major Adverse Cardiovascular Events
MedDRA	:	Medical Dictionary for Regulatory Activities
OTC	:	over the counter
PE	:	Pulmonary Embolism
PGI-C	:	Patient Global Impression of Change
PKAP	:	Pharmacokinetics Analysis Plan
PRBC	:	Packed Red Blood Cells
PSA	:	Prostate specific antigen
PT	:	Preferred Term
QW	:	Once Weekly
SAE	:	Serious Adverse Event
SAP	:	Statistical Analysis Plan
SC	:	Subcutaneous
SD	:	Standard Deviation
SF-36	:	36-Item Short Form Survey Instrument
SHBG	:	Sex hormone-binding globulin
SOC	:	System Organ Class
SOPs	:	Standard Operating Procedures
SUSAR	:	Suspected Unexpected Serious Adverse Reactions
TC	:	Testosterone cypionate
TEAEs	:	Treatment-emergent Adverse Events
TRT	:	Testosterone Replacement Therapy

TT	:	Total Testosterone
UAE	:	Unexpected adverse event
ULN	:	Upper Limit of the Normal range
WHO-DD	:	World Health Organization Drug Dictionary

1. Background Information

Testosterone is a naturally occurring steroid hormone primarily produced in the testes in males. It plays a critical role in the development of male secondary sexual characteristics, including increased muscle mass, deepened voice, and facial/body hair growth. It also contributes to bone density, libido, mood regulation, and overall metabolic function in all sexes.

Ninety-five percent (95%) of the total testosterone in males is synthesized in the Leydig cells of the testes. Defects that interfere with interactions in the hypothalamic-pituitary-testicular axis can cause male hypogonadism as well as primary testicular disorders. Such defects may be acquired or congenital. It is helpful to distinguish between primary hypogonadism (which originates in the testes) and secondary (which originates in the hypothalamus or pituitary gland). Symptoms highly suggestive of hypogonadism include decreased spontaneous erections, reduced nocturnal penile tumescence, infrequent morning erections, low libido, unexplained fatigue, and smaller testicular volume.

The normal range for early morning testosterone in a male is generally between 300 ng/dL to 1000 ng/dL, although this varies by laboratory. Hypogonadism is usually diagnosed when the morning serum testosterone level is <300 ng/dL on at least 2 occasions. Morning levels are used because testosterone levels are typically the highest.

Pharmacokinetics

Testosterone esters are less polar than free testosterone. Testosterone esters in oil, injected intramuscularly are absorbed slowly from the lipid phase; thus, testosterone cypionate (E.g. Depo Testosterone) can be given at intervals of two to four weeks.

Testosterone in plasma is 98% bound to a specific testosterone-estradiol binding globulin, and about 2 percent is free. Generally, the amount of this sex-hormone binding globulin in the plasma will determine the distribution of testosterone between free and bound forms, and the free testosterone concentration will determine its (testosterone) half-life.

- About 90% of exogenous 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 two different pathways.

- The half-life of testosterone cypionate when injected intramuscularly is approximately eight days.
- In many tissues the activity of testosterone appears to depend on reduction to dihydrotestosterone, which binds to cytosol receptor proteins. The steroid-receptor complex is transported to the nucleus where it initiates transcription events and cellular changes related to androgen action.

Pharmacokinetic Rationale for Testosterone Esters in Subcutaneous Administration

Testosterone esters, such as testosterone cypionate, are less polar than free testosterone due to the esterification of the hydroxyl group at the C17 position. This chemical modification increases lipophilicity, allowing the molecule to dissolve in oil-based vehicles and form a depot at the injection site. Amneal's proposed product is formulated in cotton seed oil at three different strengths of 50 mg, 75 mg, and 100 mg per 0.5 mL.

When administered intramuscularly, the oil-based depot allows for slow release of the esterified testosterone into systemic circulation. The ester is then hydrolyzed by esterases in the blood and tissues, releasing active free testosterone.

In subcutaneous administration, a similar depot effect occurs:

- The lipophilic ester remains in the subcutaneous fat layer longer than free testosterone would.
- Absorption is governed by diffusion from the oil phase into surrounding tissue and capillaries.
- The rate-limiting step is the release from the depot, not the hydrolysis.
- This allows for extended dosing intervals, similar to IM use.

Why This Matters for PK Study

- Depot formation in subcutaneous tissue mimics IM pharmacokinetics but may show slightly slower absorption due to lower vascularity.
- Investigators should expect:
  - A delayed Tmax compared to aqueous formulations.
  - A prolonged half-life due to sustained release.
  - Lower peak concentrations but more stable trough levels over time.
- This profile supports less frequent dosing and improved patient compliance, especially in long-

term testosterone replacement therapy.

Testosterone Binding and Its Impact on Pharmacokinetics

Testosterone in plasma exists in two primary forms:

- ~98% is bound to plasma proteins, primarily sex hormone-binding globulin (SHBG) and albumin.
- ~2% is free, representing the biologically active fraction.

◆ Role of SHBG

- SHBG has high affinity for testosterone and estradiol.
- The concentration of SHBG in plasma directly influences the distribution between bound and free testosterone.
- Factors such as age, sex, liver function, and hormonal status (e.g., estrogen levels) can alter SHBG levels.

◆ **Clinical Relevance to Subcutaneous Administration**

- The free testosterone fraction is responsible for pharmacologic activity and determines the elimination half-life.
- In subcutaneous administration of testosterone esters (e.g., testosterone cypionate):
  - The ester is slowly absorbed from the lipid depot.
  - Once in circulation, it is hydrolyzed to free testosterone.
  - The released testosterone then binds to SHBG and albumin.
- **Variability in SHBG levels** among subjects may influence:
  - Peak plasma concentrations
  - Duration of action
  - Clearance rates

Adverse Reactions

The following adverse reactions in the male have occurred with some androgens:

Endocrine and urogenital: Gynecomastia and excessive frequency and duration of penile erections. Oligospermia may occur at high dosages.

Skin and appendages: Hirsutism, male pattern of baldness, seborrhea, and acne. Cardiovascular disorders: Myocardial infarction, stroke.

Fluid and electrolyte disturbances: Retention of sodium, chloride, water, potassium, calcium, and inorganic phosphates.

Gastrointestinal: Nausea, cholestatic jaundice, alterations in liver function tests, rarely hepatocellular neoplasms and peliosis hepatis.

Hematologic: Suppression of clotting factors II, V, VII, and X, bleeding in patients on concomitant anticoagulant therapy, and polycythemia.

Nervous system: Increased or decreased libido, headache, anxiety, depression, and generalized paresthesia.

Allergic: Hypersensitivity, including skin manifestations and anaphylactoid reactions. Vascular disorders: Venous thromboembolism.

Special senses: Rare cases of central serous chorioretinopathy (CSCR).

Miscellaneous: Inflammation and pain at the site of intramuscular injection.

Drug Interactions:

Androgens may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may require reduction in order to maintain satisfactory therapeutic hypoprothrombinemia.

Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.

In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirements.

Warnings and Precautions

Hypercalcemia may occur in immobilized patients. If this occurs, the drug should be discontinued.

Prolonged use of high doses of androgens (principally the 17-α alkyl-androgens) has been associated with

development of hepatic adenomas, hepatocellular carcinoma, and peliosis hepatis —all potentially life-threatening complications.

Geriatric patients treated with androgens may be at an increased risk of developing prostatic hypertrophy and prostatic carcinoma although conclusive evidence to support this concept is lacking.

There have been postmarketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products, such as testosterone cypionate. Evaluate patients who report symptoms of pain, edema, warmth and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous thromboembolic event is suspected, discontinue treatment with testosterone cypionate and initiate appropriate workup and management.

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), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the use of testosterone compared to non-use. 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 Testosterone Cypionate Injection.

Testosterone has been participant to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids. Anabolic androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions.

If testosterone abuse is suspected, check serum testosterone concentrations to ensure they are within therapeutic range. However, testosterone levels may be in the normal or subnormal range in men abusing synthetic testosterone derivatives. Counsel patients concerning the serious adverse reactions associated with abuse of testosterone and anabolic androgenic steroids. Conversely, consider the possibility of testosterone and anabolic androgenic steroid abuse in suspected patients who present with serious cardiovascular or psychiatric adverse events.

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 persists in patients being treated for hypogonadism.

The preservative benzyl alcohol has been associated with serious adverse events, including the "gasping syndrome", and death in pediatric patients. Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the liver and kidneys' capacity to detoxify the chemical. Premature and low-birth weight infants may be more likely to develop toxicity.

Androgen therapy should be used cautiously in healthy males with delayed puberty. The effect on bone maturation should be monitored by assessing bone age of the wrist and hand every 6 months. In children, androgen treatment may accelerate bone maturation without producing compensatory gain in linear growth. This adverse effect may result in compromised adult stature. The younger the child the greater the risk of compromising final mature height.

This drug has not been shown to be safe and effective for the enhancement of athletic performance. Because of the potential risk of serious adverse health effects, this drug should not be used for such purpose.

2. Study Objectives and Endpoints

OBJECTIVES
Primary Objective: To evaluate the safety and efficacy of Testosterone Cypionate auto-injector administered subcutaneously once each week via an auto-injector over a 24-week treatment period in adult males with hypogonadism. **Secondary Objectives:** • To evaluate the usability of auto-injector and accompanying Instructions for use. • To characterize the response of Total Testosterone concentrations to dose adjustment • To further evaluate the safety and tolerability of testosterone cypionate administered subcutaneously once weekly via an auto-injector beyond the 24-week primary evaluation period.
PRIMARY ENDPOINT
The primary efficacy endpoint in the study will be the percentage of participants at week 12 with average serum Total Testosterone concentration ($C_{avg\ 0\text{-}168h}$) over the 7-day dosing interval (0-168 hours) to be within the defined range of 300 to 1100 ng/dL using full PK population data. The primary endpoint will be satisfied if ≥75% of participants have serum Total Testosterone $C_{avg168h}$ within the range of 300 to 1100 ng/dL at Week 12, with a lower bound of the 95% confidence interval (CI) at ≥65%. The primary efficacy endpoint, Cavg 168h, is calculated from the AUC using the following formula; Cavg 168h = AUC (0-168 h) / 168
KEY SAFETY ENDPOINTS
i. Percentage of participants with maximum (peak) serum Total Testosterone concentration (C_{max}) <1500 ng/dL. This endpoint will be satisfied if ≥85% of participants have serum Total Testosterone C_{max} <1500 ng/dL at Week 12 of treatment. ii. Percentage of participants with serum Total Testosterone C_{max} between 1800 to 2500 ng/dL

(inclusive). This endpoint will be satisfied if <5% of participants have serum Total Testosterone C_{max} in the range of 1800 to 2500 ng/dL at Week 12 of treatment. iii. Number of participants with serum Total Testosterone C_{max} >2500 ng/dL. This endpoint will be satisfied if no participants have serum Total Testosterone C_{max} >2500 ng/dL at Week 12 of treatment.
Additional Secondary Efficacy Analysis
i. Number and percentage of participants with minimum serum concentration (C_{min}) of Total Testosterone <300 ng/dL at Week 12 of treatment. ii. Serum Testosterone $C_{avg168h}$ within the defined range of 300 to 1100 ng/dL for the 75 mg dose (that is, excluding participants on the 50 mg and 100 mg dose) at Week 12. Endpoint will be satisfied if ≥75% of participants with a lower limit of the 95% CI ≥65%, have serum Total Testosterone Cavg168h within the defined range of 300 to 1100 ng/dL at Week 12 of treatment. iii. Assuming sufficient numbers of participants received the 100 mg dose of the auto-injector, the serum Total Testosterone $C_{avg168h}$ at Week 12 will be calculated and presented with descriptive statistics. iv. Assuming sufficient numbers of participants received the 50 mg dose of the auto-injector, the serum Total Testosterone $C_{avg168h}$ at Week 12 will be calculated and presented with descriptive statistics. v. Single-dose area under the curve (AUC), Cmax, time to maximum serum concentration (Tmax) of Total Testosterone, and Cavg168h for the 75 mg dose of the auto-injector at week 1 (with PK Population data).
SAFETY ENDPOINTS
• Number (percent), severity, and relatability of adverse events (AEs) and serious adverse events (SAEs) • Vital signs (Pulse rate, Axillary body Temperature, Respiratory rate, Blood pressure) • ECG • Physical examinations, including Digital Rectal Exam (DRE)-if performed • Laboratory assessments (excluding serology) will be performed from baseline through the 24-week primary evaluation period and may continue at scheduled visits thereafter. • Use of anti-hypertensive medications (new initiation or dose adjustment) from baseline to through

the 24-week primary evaluation period and may continue at scheduled visits thereafter.

- Change from baseline in 24-hour mean systolic and diastolic blood pressure measured by continuous ABPM at Week 12, week 24, and scheduled visits thereafter.
- Change from baseline in quality of life based on C-SSRS, HDRS, SIAQ, SF-36 Assessment of Essential Tasks Questionnaire at week 24, and scheduled visits thereafter.

3. Trial Design

3.1 Study Design

This is a Phase 3, Multi-Center, Single-Blind (with respect to dose strength), Single-Arm, Multiple-Dose Study Evaluating the Safety and Efficacy of Testosterone Cypionate Administered Subcutaneously via a Weekly Auto-Injector in Adult Males With Hypogonadism Through Week 24. Subjects may continue in a safety follow-up period beyond the 24-week.

Throughout the study, the principal investigator (PI) and additional staff member (at the PI's discretion) of the clinical site will remain unblinded to the testosterone cypionate dosage for the participant safety monitoring and dosage adjustment purposes based on periodic serum total testosterone levels, as applicable. Study participants, and the clinical staff responsible for conducting study assessments will remain blinded to the assigned dosage strength in order to minimize assessment, observation, and reporting bias.

This study includes an approximately 4-week (28-days) screening period followed by a 24-week primary treatment and evaluation period to assess the safety and efficacy of testosterone cypionate administered subcutaneously once weekly via an auto-injector (50 mg, 75 mg, and 100 mg) in adult males with hypogonadism.

Subjects who complete the 24-week primary evaluation period may continue treatment thereafter, with ongoing safety assessment at scheduled visits (refer to Figure 3.1 for a schematic representation of the study design). Assessments will be performed as outlined in Section 17.1 (Schedule of Assessments).

During the screening phase, before conducting comprehensive clinical laboratory assessments, all the participants undergo at least one (1) qualifying serum testosterone concentration measurements to confirm hypogonadal status along with HbA1c and PSA evaluation. Participants meeting this preliminary study requirement, may then proceed to comprehensive clinical laboratory assessments as per the protocol.

The primary endpoints of this study are as follows:

The primary efficacy endpoint in the study will be percentage of participants at week 12 with average serum Testosterone concentration ($C_{avg\ 0\text{-}168h}$) over the 7-day dosing interval (0-168 hours) to be within the defined range of 300 to 1100 ng/dL using full PK population data.

After informed consent has been obtained, participants having at least two serum Testosterone values <300

ng/dL obtained in the morning (07:30 AM - 10:00 AM) during the screening phase on two separate days at least 72 hours apart approximately 28 days prior to dosing, One repeat total T concentration will be allowed if 1 of the 2 morning total T concentrations is ≥300 ng/dL and meeting the study eligibility criteria enter the study.

Figure 3.1: Schematic Representation of Study Design

Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7, 9, 11, 13, 15	Visit 8, 10, 12, 14, 16	Visit 17	Follow Up
	Week 1	**Week 6**	**Week 7**	**Week 12**	**Week 13**	**Week 18, 24, 30, 36, & 42**	**Week 19, 25, 31, 37, and 43**	**Week 52**	**Week 53-54**
Day -28 to -1 (approx)	**Day 1**	**Day 36**	**Day 43**	**Day 78**	**Day 85**	**Day 120, 162, 204, 246, & 288**	**Day 127, 169 211, 253, & 295**	**Day 358**	**7-14 days**
Screening	Dosing all eligible participants with 75 mg strength of the Test Product **Pre-dose or Full PK Sampling (45 participants)**	Weeks 4-6: C_{trough} sampling or **Full PK Sampling (45 participants)**		Weeks 9-11: C_{trough} sampling **PK Sampling (all participants)**			Week 31 and week 43 dose titration is at the discretion of PI.		
	TT C_{trough} → TT C_{trough} ≥650 ng/dL → Decrease dose by 25 mg → TT C_{trough} ≥650 ng/dL → Decrease dose by 25 mg → TT C_{trough} ≥650 ng/dL → Decrease dose by 25 mg TT C_{trough} <350 ng/dL → Increase dose by 25 mg → TT C_{trough} <350 ng/dL → Increase dose by 25 mg → TT C_{trough} <350 ng/dL → Increase dose by 25 mg TT C_{trough} b≥350-<650 ng/dL → No change in Dose → TT C_{trough} ≥350-<650 ng/dL → No change in Dose → TT C_{trough} ≥350-<650 ng/dL → No change in Dose								
	Treatment Phase				Treatment Phase and Continued Safety Follow Up				**Post Treatment Follow-Up**
	Dose assignment by IWRS (Double-blind for dosage strength)				**End of Treatment**				**End of Study**

Blood samples for PK analysis of TT, DHT, DHTC, E2 and Testosterone Cypionate will be obtained prior to dosing and at specified times up to 168 hours post dose at week 1, 6 and/ or week 12.

3.2 Study Visits and Procedures

The study will be conducted in three (3) phases:

Screening Phase (Approximately 4 weeks)

- **Visit 1: Screening**
  - Visit 1a: Testosterone qualification assessment
  - Visit 1b: Testosterone qualification assessment
  - Visit 1c: Additional qualification assessment (if required)

Treatment Phase (Primary Evaluation Period: Through Week 24)

- Visit 2: Week 1 (Day 1) – Initiation of treatment
- Visit 3: Week 6 (Day 36)
- Visit 4: Week 7 (Day 43) – Dose titration (if required)
- Visit 5: Week 12 (Day 78) – (Evaluation of Primary Efficacy)
- Visit 6: Week 13 (Day 85) – Dose titration (if required)
- Visit 7: Week 18 (Day 120)
- Visit 8: Week 19 (Day 127) – Dose titration (if required)
- Visit 9: Week 24 (Day 162) – End of primary safety and efficacy evaluation

---

Continued Safety Follow-Up (Beyond Week 24)

- Visit 10: Week 25 (Day 169) – Dose titration (if required)
- Visit 11: Week 30 (Day 204)
- Visit 12: Week 31 (Day 211) –
- Visit 13: Week 36 (Day 246)
- Visit 14: Week 37 (Day 253) – Dose titration (if required)

- Visit 15: Week 42 (Day 288)
- Visit 16: Week 43 (Day 295) –
- Visit 17: Week 52 (Day 358) – End of treatment or Study Completion for subjects who continue participation

---

Follow-Up

- **Visit 18: Follow-up visit (7–14 days after last dose)**

Window period

- All scheduled study activities should be performed on the designated study days. However, a visit window of ±2 days will be permitted for weekly dose administration and the corresponding study assessments from week 2 onward, except for the Week 12 dose administration, full PK sampling, and associated assessments.
- The ±2-day visit window is not applicable to Week 12 dose administration for any subject. The Week 12 dose must be administered on the same weekday as the Week 1 dose administration.
- For the subset of 45 subjects participating in the intensive PK sampling schedule at Weeks 1 and 6, the ±2-day visit window is applicable only to Weeks 2, 3, 4, 5, and Weeks 7, 8, 9, 10, and 11. The Week 6 visit, including dose administration, full PK sampling, and all associated assessments, must be conducted on the scheduled study day without any visit window.
- Whenever the ±2-day visit window is used for any weekly visit, subsequent weekly dose administrations must be rescheduled to the original Week 1 dosing weekday. The visit window does not permanently shift the dosing schedule.

Dose	Date of administration (Week day)
Week 1	Actual: 03/Aug/2026 (Monday)
Week 4	Schedule: 24/Aug/2026 (Monday)
Example 1, if window period of +2 days is used for week 4	
Week 4	Actual: 26/Aug/2026 (Wednesday)
Week 5	Schedule: 31/Aug/2026 (Monday) **and not 02/Sep/2026 (Wednesday)**
Example 2, if window period of -2 days is used for week 4	
Week 4	Actual: 22/Aug/2026 (Saturday)
Week 5	Schedule: 31/Aug/2026 (Monday) **and not 29/Aug/2026 (Saturday)**

- A visit window of ±2 days will also be permitted for C_{trough} sample required for dose titration at Week 6, 18, 24, and scheduled visits thereafter, and PK steady-state sample collection scheduled at Weeks 4, 5, 6 (except for the 45 subjects undergoing full PK sampling), 9, 10, and week 11.
- The visit window for PK sample collection and other scheduled study assessments will remain the same and will be referenced to the actual dosing time at the respective visit.

The total duration of study participation for each subject will be up to 58 weeks, including an approximately 4-week screening period, a 24-week primary treatment and evaluation period, continued treatment with ongoing safety assessment beyond Week 24, and a follow-up visit 7 to 14 days after the last dose.

Voluntarily given informed consent will be obtained from each participant and /or Legally Authorized Representative (LAR) before commencing any study-specific procedures. After obtaining informed consent, the participant will be checked for eligibility according to the inclusion and exclusion criteria. Consenting and eligible participants will be enrolled to enter the Treatment Initiation Visit as per the discretion of the Investigator.

3.2.1 Study Conduct

3.2.1.1 Screening Phase

Visit 1:

During the screening phase, before conducting comprehensive clinical laboratory assessments, all the participants undergo at least one (1) qualifying serum testosterone concentration measurements to confirm hypogonadal status along with HbA1c and PSA evaluation. Participants meeting this preliminary study requirement, may then proceed to comprehensive clinical laboratory assessments as per the protocol.

Hypogonadal adult male participants aged 18-75 years with the BMI range of 18.5 to 39.9 kg/m^2, inclusive, will be selected according to below criteria

- Informed Consent Process: All participants will be asked to provide written informed consent (ICF) before participating in the study.
- Recording and Evaluation of medical and surgical history: The medical history, including hypogonadism, will be obtained
- Medication history check: Hypogonadism medication history, prior and concomitant/ Prohibited medication; to ensure that washout of all medications is maintained
- Collection of Demographic information [including age, ethnicity, race, gender (male)], height, weight and BMI.
- Recording of physical examination, including digital rectal exam will be performed
- Recording of Vitals (Pulse Rate, Blood pressure (SBP and DBP), Axillary Body Temperature, Respiratory Rate)
- ECG, Clinical laboratory tests for prostate-specific antigen test, Endocrine function assessment Biochemistry, Hematology, coagulation tests, albumin, SHBG, for diabetic patients-HbA1c, Serology, and Urine analysis including Urine drug abuse test.
- Blood sample for serum total testosterone at bioanalytical facility for informative purpose
- International Prostate Symptom Score (I-PSS) assessment

- Participant will be registered in IWRS
- Concomitant medication review
- Adverse event collection

Visit 1a: Testosterone Qualification 1a (TT Qual 1a)

- Vital signs, adverse event collection and concomitant medication review will be performed at this visit along with total testosterone estimation in serum, and blood sample for serum total testosterone at bioanalytical facility for informative purpose

Visit 1b: Testosterone Qualification 1b (TT Qual 1b)

- Vital signs, adverse event collection and concomitant medication review will be performed at this visit along with total testosterone estimation in serum, and blood sample for serum total testosterone at bioanalytical facility for informative purpose.

Visit 1c: Testosterone Qualification 1c (TT Qual 1c)- if required

Vital signs, adverse event collection and concomitant medication review will be performed at this visit along with total testosterone estimation in serum & blood sample for serum total testosterone at bioanalytical facility for informative purpose, if required

Participants who have 1 sample >300 ng/dL may have 1 retest for TT concentrations (Visit 1c) which must occur no less than 7 days after the previous test. After retesting, if 2 of the 3 TT concentrations are <300 ng/dL, the participant will be eligible to participate in the study.

3.2.1.2 Treatment Phase (Primary Evaluation Period: Through Week 24)

Participants meeting all of the inclusion criteria and none of the exclusion criteria during screening period will enter into Treatment Period.

Visit 2: Week 1 (Initiation of Treatment)

- On Day 1 of week 1 the following assessments will be performed:

- Participants* will be Checked-in to facility at least 10 hours before baseline PK blood sampling time point and housed (domicile) up to 24 hours post-dose.

*: is applicable for 45 participants who are willing for full PK sampling will be domiciled, rest all can be ambulatory for this visit

- Symptom based physical examination
- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature, Respiratory rate))
- Urine drug abuse test
- ECG, Clinical laboratory assessment of Endocrine function, PSA, Biochemistry, Hematology, Urine analysis, Coagulation tests, albumin, SHBG, and for diabetic patients-HbA1c
- Verification of all eligibility criteria
- I-PSS
- Aging Males' Symptoms (AMS)- (applicable for only to participants aged 40 years or older)
- Patient Global Impression of Change (PGI C)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Hamilton Depression Rating Scale (HDRS)
- 36-Item Short Form Survey Instrument (SF-36)
- Self-Injection Assessment Questionnaire (SIAQ),
- Assessment of Essential Tasks Questionnaire
- IP dispensing will be done via IWRS for the first weeks 1 to 6
- Continuous Ambulatory Blood Pressure Monitoring (24 h) from 0.5 hours pre-dose to 24 h post-dose
  This could be performed during domicile or ambulatory on week -1 to day 1, but to be completed before day 1/week 1 dose administration for all participants.
- Dose administration to participants by study personnel
- Injection site assessment
  Injection sites will be evaluated for injection site reactions (such as pain, itching, redness and swelling). The injection site will be monitored for any skin irritation before dosing (within 30 minutes) and any reactions after dosing at 0.50, 01.00, (± 15 minutes), 24.00* (within ± 30 minutes for in house assessments), 36.00*, and 48.00* hours (± 2 h).

Note: Photographs will be captured only for subjects who experience ISTR (Injection site reaction). For subjects/ participants who experience ISTR, photographs will be captured at: 0.50, 01.00, 24.00*, 36.00*, and 48.00* hours post dose even if ISTR is resolved earlier.

**: is applicable for 45 participants.*

- PK profile blood collection (TT, DHT, DHTC, E2 and Testosterone Cypionate) as per the following scheduled time points: 0.00 (pre-dose), 0.50, 3.00, 6.00, 9.00, 12.00 h - *applicable for 45 participants For the rest of the participants, only 0.00 pre-dose sample will be collected.*
- Autoinjector device training and assessment of self- administration essential tasks by study staff along with verbal instructions.
- Concomitant medication review
- Monitoring of Adverse Events
- Meal will be provided [please refer "Study Assessments and Schedule of Events of TREATMENT PHASE"]- *is applicable for 45 participants, who are willing for full PK sampling.*
- Issue of Diary for Dose-administration and compliance (to be recorded by the participant for all self-administrations from week 2)
- Issue of Diary for glucose (to record glucose level by the participant from week 1) and Glucometer and strips for diabetic patients
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7)
- Issue of study drugs to the participants for the weeks 2, 3, 4 & 5 for self-administration

➢ <u>On Day 2, 3, 4 of week 1 the following assessments will be performed *(applicable for 45 participants)*</u>

- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature)
- PK profile blood collection (TT, DHT, DHTC, E2 and Testosterone Cypionate) as per the following scheduled time points: 24.00 (day 2), 48.00 (day 3), and 72.00 h (day 4)

Week 2: applicable only for 45 participants

➢ Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature)

- PK profile blood collection (TT, DHT, DHTC, E2 and Testosterone Cypionate); 168.00 h (day 8)

Note: Day 8 of Week 1 corresponds to the day 1 of week 2 visit for the treatment phase. Obtain the 168

hr post-dose PK sample on this day before dosing.

- Self-Dose administration*
- Injection site assessment

  Injection site will be evaluated for ISTR (such as pain, itching, redness and swelling). The injection site will be monitored for any skin irritation within 0.50 and 1.00 hours (within ± 15 minutes) of dosing.

  Note: Photographs will be captured only for subjects who experience ISTR (Injection site reaction). For subjects who experience ISTR, photographs will be captured even if ISTR is resolved earlier.
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7)*

  *: applicable for all participants

Week 3:

- Self-Dose administration
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7) in the diary.

Week 4:

- Testosterone C_{trough} PK Blood sampling (sampling will be conducted before dose administration)
- Self-Dose administration
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7).

Week 5:

- Testosterone C_{trough} PK Blood sampling (sampling will be conducted before dose administration).
- Self-Dose administration
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7)

Visit 3: Week 6 (Trough Determination):

➢ <u>On Day 1 of week 6 the following assessments will be performed:</u>

- Participants* will be Checked-in to facility at least 10 hours before baseline PK blood sampling time point and housed (domicile) up to 24 hours post-dose.

  **: is applicable for 45 participants who are willing for full PK sampling will be domiciled, rest all will be ambulatory for this visit*

- Symptom based physical examination
- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature, Respiratory rate)
- Recording of concomitant medication administration or AEs if any
- Diary review IP accountability and compliance check and blood glucose monitoring (if applicable)
- Urine drug abuse test
- Testosterone C_{trough} Blood sampling (sampling will be conducted before dose administration) for week 7 dose titration, albumin, SHBG, at central lab.
- PK profile blood collection (TT, DHT, DHTC, E2 and Testosterone Cypionate) as per the following scheduled time points0.00 (pre-dose), 0.50, 3.00, 6.00, 9.00, 12.00 h - *applicable for 45 participants*
- Testosterone C_{trough} PK Blood sampling (sampling will be conducted before dose administration) for the rest of the participants
- Self-Dose administration
- Injection site assessment:

  Injection site will be evaluated for injection site reactions (such as pain, itching, redness and swelling). The injection site will be monitored for any skin irritation 0.50, and 1.00 hours after dosing at (within ± 15 minutes).

  Note: Photographs will be captured only for subjects who experience ISTR (Injection site reaction). For subjects who experience ISTR, photographs will be captured even if ISTR is resolved earlier.
- Meal will be provided [please refer "Study Assessments and Schedule of Events of TREATMENT PHASE"]- *is applicable for 45 participants, who are willing for full PK sampling.*
- Issue of Glucometer and /or strips for diabetic patients
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7)

➢ <u>On Day 2, 3, 4, 7 of week 6 the following assessments will be performed *(applicable for 45 participants)*</u>

- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature)
- PK profile blood collection (TT, DHT, DHTC, E2 and Testosterone Cypionate) as per the following scheduled time points: 24.00 (day 2), 48.00 (day 3), 72.00 (day 4), and 144.00 h (day 7).

Visit 4: Week 7 (Dose titration):

➢ <u>On Day 1 of week 7 the following assessments will be performed:</u>

- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature, Respiratory rate)
- PK profile blood collection* (TT, DHT, DHTC, E2 and Testosterone Cypionate); 168.00 h (day 8)

  Note: Day 8 of Week 6 corresponds to the day 1 of week 7 visit for the treatment phase. Obtain the 168 hr post-dose PK sample on this day before dosing

  *: applicable only for 45 participants
- Recording of concomitant medication administration or AEs if any
- Titrate dose via IWRS, if required, based on Testosterone C_{trough} Blood sampling of week 6
- IP dispensing via IWRS for the weeks 7 to 12
- Self-Dose administration
- Injection site assessment:

  Injection site will be evaluated for injection site reactions (such as pain, itching, redness and swelling). The injection site will be monitored for any skin irritation 0.50, and 1.00 hours after dosing (within ± 15 minutes).

  Note: Photographs will be captured only for subjects who experience ISTR (Injection site reaction). For subjects who experience ISTR, photographs will be captured even if ISTR is resolved earlier.
- Issue of study drugs to the participants for the week 8, 9, 10, & 11 for self-administration.
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7).

Weeks 8-11:

- Testosterone C_{trough} PK Blood sampling (sampling will be conducted before dose administration of weeks 9-11)
- Self-Dose administration
- Glucose monitoring (self-monitoring once weekly,) for diabetic patients (between day 2 to day 7).

Visit 5: Week 12 (Pivotal PK Sampling and Trough Determination):

➢ <u>On Day 1 of week 12 the following assessments will be performed:</u>

- Participant will be Checked-in to facility at least 10 hours before for baseline PK blood sampling time

point and housed up to 24.00 hours.

- Physical examination (DRE may be performed after dosing as per investigator's discretion)
- Weight and BMI (using screening height)
- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature, Respiratory rate)
- Urine drug abuse test
- ECG, Clinical laboratory assessment of Endocrine function, PSA, Biochemistry, Hematology, Urine analysis, Coagulation tests, albumin, SHBG, and for diabetic patients-HbA1c will be performed
- Recording of concomitant medication administration or AEs if any
- Diary review for IP accountability, and compliance and glucose monitoring (if applicable)
- Testosterone C_{trough} Blood sampling (sampling will be conducted before dose administration for week 13 dose titration) at central lab.
- Self-Dose administration
- Injection site assessment: Injection sites will be evaluated for injection site reactions (such as pain, itching, redness and swelling). The injection site will be monitored for any skin irritation before dosing (within 30 minutes) and any reactions after dosing at 0.50, 1.00 (within ± 15 minutes), 24.00 (within ± 30 minutes) hours post dose.

  Note: Photographs will be captured only for subjects who experience ISTR (Injection site reaction). For subjects who experience ISTR, photographs will be captured at: 0.50, 1.00, 24.00 hours post dose even if ISTR is resolved earlier.
- Continuous Ambulatory Blood Pressure Monitoring (from 0.5 hours pre-dose to 24 hours post-dose)
- PK profile blood collection (TT, DHT, DHTC, E2 and Testosterone Cypionate) as per the following scheduled time points: 0.00 (pre-dose), 3.00, 6.00, 9.00, 12.00 h.
- Meal will be provided [please refer "Study Assessments and Schedule of Events of TREATMENT PHASE"]

➢ <u>On Day 2, 3, 4, 5, 6, 7 of week 12, the following assessments will be performed:</u>

- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature, Respiratory rate)
- PK profile Blood collection (TT, DHT, DHTC, E2 and Testosterone Cypionate) as per the following

scheduled time points 24.00 and 36.00 (day 2), 48.00 (day 3), 72.00 (day 4), 96.00 (day 5), 120.00 (day 6), and 144.00 (day 7) h.

- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7)

Visit 6: Week 13

➢ <u>On Day 1 of week 13 the following assessments will be performed:</u>

- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature, Respiratory rate)
- PK profile blood collection (TT, DHT, DHTC, E2 and Testosterone Cypionate); 168.00 h (day 8).
  Note: Day 8 of Week 12 corresponds to the week 13 visit for the treatment phase. Obtain the 168 hr post-dose PK sample on this day before dosing.
- Recording of concomitant medication administration or AEs if any
- Titrate dose via IWRS, if required, based on Testosterone C_{trough} Blood sampling of week 12
- IP dispensing via IWRS for the weeks 13 to 18
- Self-Dose administration
- Injection site assessment:
  Injection site will be evaluated for injection site reactions (such as pain, itching, redness and swelling). The injection site will be monitored for any skin irritation 0.5 and 1.00 hours after dosing.

Note: Photographs will be captured only for subjects who experience ISTR (Injection site reaction). For subjects who experience ISTR, photographs will be captured even if ISTR is resolved earlier.

- Issue of study drugs to the participants for the weeks 14, 15, 16 & 17.
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7)
- Issue of Glucometer and / or strips for diabetic patients

Weeks 14-17

- Self-Dose administration
- Recording of self-drug administration (for the weeks 14-17) and Glucose monitoring (self-monitoring once weekly, for the weeks 14 to 17) for diabetic patients (between day 2 to day 7).

Visit 7: Week 18

- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature, Respiratory rate)
- Symptom based physical examination
- Urine drug abuse test
- Testosterone C_{trough} Blood sampling (sampling will be conducted before dose administration for week 19 dose titration), albumin, SHBG at central lab and blood sample for serum TT at bioanalytical facility for informative purpose.
- Diary review for IP accountability and compliance and glucose monitoring (if applicable)
- Recording of concomitant medication administration or AEs, if any
- Self-Dose administration
- Injection site assessment

  Injection site will be evaluated for ISTR (such as pain, itching, redness and swelling). The injection site will be monitored for any skin irritation within 0.50 and 1.00 hours (within ± 15 minutes) of dosing.

  Note: Photographs will be captured only for subjects who experience ISTR (Injection site reaction). For subjects who experience ISTR, photographs will be captured even if ISTR is resolved earlier.
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7)

Visit 8: Week 19

- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature, Respiratory rate)
- Recording of concomitant medication administration or AEs if any
- Titrate dose via IWRS, if required, based on Testosterone C_{trough} Blood sampling of week 18
- IP dispensing via IWRS for the weeks 19 to 24.
- Self-Dose administration
- Injection site assessment

  Injection site will be evaluated for ISTR (such as pain, itching, redness and swelling). The injection site will be monitored for any skin irritation within 0.50 and 1.00 hours (within ± 15 minutes) of dosing.

  Note: Photographs will be captured only for subjects who experience ISTR (Injection site reaction). For subjects who experience ISTR, photographs will be captured even if ISTR is resolved earlier.

- Issue of study drugs to the participants for the weeks 20, 21, 22 & 23.
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7)
- Issue of Glucometer and / or strips for diabetic patients

Weeks 20-23

- Self-Dose administration
- Recording of self-drug administration (for the weeks 20 to 23) and Glucose monitoring (self-monitoring once weekly, for the weeks 20 to 23) for diabetic patients (between day 2 to day 7)

Visit 9: Week 24 (End of primary safety assessment)

- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature, Respiratory rate)
- Physical examination (DRE may be performed after dosing as per investigator's discretion)
- Weight and BMI
- Urine drug abuse test
- ECG, Clinical laboratory assessment of Endocrine function, PSA, Biochemistry, Coagulation tests, Hematology, Urine analysis, albumin, SHBG, and for diabetic patients-HbA1c
- Testosterone C_{trough} Blood sampling (sampling will be conducted before dose administration for week 25 dose titration) at central lab and blood sample for serum TT at bioanalytical facility for informative purpose.
- Diary review for IP accountability and compliance and glucose monitoring (if applicable)
- Recording of concomitant medication administration or AEs, if any
- I-PSS
- Aging Males' Symptoms (AMS) (applicable only to participants aged 40 years or older)
- Patient Global Impression of Change (PGI-C)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Hamilton Depression Rating Scale (HDRS)
- 36-Item Short Form Survey Instrument (SF-36)
- Self-Injection Assessment Questionnaire (SIAQ),

- Assessment of Essential Tasks Questionnaire
- Continuous Ambulatory Blood Pressure Monitoring (from 0.5 hours pre-dose to 24 hours post-dose)
- Self-Dose administration
- Injection site assessment

  Injection site will be evaluated for ISTR (such as pain, itching, redness and swelling). The injection site will be monitored for any skin irritation within 0.50 and 1.00 hours (within ± 15 minutes) of dosing.

  Note: Photographs will be captured only for subjects who experience ISTR (Injection site reaction). For subjects who experience ISTR, photographs will be captured even if ISTR is resolved earlier.
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7)

3.2.1.3 Continued Safety Follow-Up (Beyond Week 24)

Visit 10: Week 25

- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature, Respiratory rate)
- Recording of concomitant medication administration or AEs if any
- Titrate dose via IWRS, if required, based on Testosterone C_{trough} Blood sampling of week 24
- IP dispensing via IWRS for the weeks 25 to 30.
- Self-Dose administration
- Injection site assessment

  Injection site will be evaluated for ISTR (such as pain, itching, redness and swelling). The injection site will be monitored for any skin irritation within 0.50 and 1.00 hours (within ± 15 minutes) of dosing.

  Note: Photographs will be captured only for subjects who experience ISTR (Injection site reaction). For subjects who experience ISTR, photographs will be captured even if ISTR is resolved earlier.
- Issue of study drugs to the participants for the weeks 26, 27, 28 & 29.
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7)
- Issue of Glucometer and / or strips for diabetic patients

Weeks 26-29

- Self-Dose administration

- Recording of self-drug administration (for the weeks 26 to 29) and Glucose monitoring (self-monitoring once weekly, for the weeks 26 to 29) for diabetic patients (between day 2 to day 7)

Visit 11: Week 30

- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature, Respiratory rate)
- Symptom based physical examination
- Urine drug abuse test
- Testosterone C_{trough} Blood sampling (sampling will be conducted before dose administration for week 31 dose titration), albumin, SHBG at central lab and blood sample for serum TT at bioanalytical facility for informative purpose.
- Diary review for IP accountability and compliance and glucose monitoring (if applicable)
- Recording of concomitant medication administration or AEs, if any
- Self-Dose administration
- Injection site assessment

  Injection site will be evaluated for ISTR (such as pain, itching, redness and swelling). The injection site will be monitored for any skin irritation within 0.50 and 1.00 hours (within ± 15 minutes) of dosing.

  Note: Photographs will be captured only for subjects who experience ISTR (Injection site reaction). For subjects who experience ISTR, photographs will be captured even if ISTR is resolved earlier.
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7)

Visit 12: Week 31

- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature, Respiratory rate)
- Recording of concomitant medication administration or AEs if any
- Titrate dose via IWRS, if required at the discretion of PI, based on Testosterone C_{trough} Blood sampling of week 30
- IP dispensing via IWRS for the weeks 31 to 36.
- Self-Dose administration
- Injection site assessment

  Injection site will be evaluated for ISTR (such as pain, itching, redness and swelling). The injection site

will be monitored for any skin irritation within 0.50 and 1.00 hours (within ± 15 minutes) of dosing.

Note: Photographs will be captured only for subjects who experience ISTR (Injection site reaction). For subjects who experience ISTR, photographs will be captured even if ISTR is resolved earlier.

- Issue of study drugs to the participants for the weeks 32, 33, 34 & 35.
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7)
- Issue of Glucometer and / or strips for diabetic patients

Weeks 32-35

- Self-Dose administration
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7)

Visit 13: Week 36

- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature, Respiratory rate)
- Physical examination (DRE may be performed after dosing as per investigator's discretion)
- Weight and BMI
- Urine drug abuse test
- ECG, Clinical laboratory assessment of Endocrine function, PSA, Biochemistry, Coagulation tests, Hematology, Urine analysis, albumin, SHBG, and for diabetic patients-HbA1c
- Testosterone C_{trough} Blood sampling (sampling will be conducted before dose administration for week 37 dose titration) at central lab and blood sample for serum TT at bioanalytical facility for informative purpose.
- Diary review for IP accountability and compliance and glucose monitoring (if applicable)
- Recording of concomitant medication administration or AEs, if any
- Self-Dose administration
- Injection site assessment

  Injection site will be evaluated for ISTR (such as pain, itching, redness and swelling). The injection site will be monitored for any skin irritation within 0.50 and 1.00 hours (within ± 15 minutes) of dosing.

  Note: Photographs will be captured only for subjects who experience ISTR (Injection site reaction). For subjects who experience ISTR, photographs will be captured even if ISTR is resolved earlier.

- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7)

Visit 14: Week 37

- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature, Respiratory rate)
- Recording of concomitant medication administration or AEs if any
- Titrate dose via IWRS, if required, based on Testosterone C_{trough} Blood sampling of week 36
- IP dispensing via IWRS for the weeks 37 to 42.
- Self-Dose administration
- Injection site assessment

  Injection site will be evaluated for ISTR (such as pain, itching, redness and swelling). The injection site will be monitored for any skin irritation within 0.50 and 1.00 hours (within ± 15 minutes) of dosing.

  Note: Photographs will be captured only for subjects who experience ISTR (Injection site reaction). For subjects who experience ISTR, photographs will be captured even if ISTR is resolved earlier.
- Issue of study drugs to the participants for the weeks 38, 39, 40 & 41.
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7)
- Issue of Glucometer and / or strips for diabetic patients

Weeks 38-41

- Self-Dose administration
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7)

Visit 15: Week 42

- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature, Respiratory rate)
- Symptom based physical examination
- Urine drug abuse test
- Testosterone C_{trough} Blood sampling (sampling will be conducted before dose administration for week 43 dose titration), albumin, SHBG at central lab and blood sample for serum TT at bioanalytical facility for informative purpose.
- Diary review for IP accountability and compliance and glucose monitoring (if applicable)

- Recording of concomitant medication administration or AEs, if any
- Self-Dose administration
- Injection site assessment

  Injection site will be evaluated for ISTR (such as pain, itching, redness and swelling). The injection site will be monitored for any skin irritation within 0.50 and 1.00 hours (within ± 15 minutes) of dosing.

  Note: Photographs will be captured only for subjects who experience ISTR (Injection site reaction). For subjects who experience ISTR, photographs will be captured even if ISTR is resolved earlier.
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7)

Visit 16: Week 43

- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature, Respiratory rate)
- Recording of concomitant medication administration or AEs if any
- Titrate dose via IWRS, if required at the discretion of PI, based on Testosterone C_{trough} Blood sampling of week 42
- IP dispensing via IWRS for the weeks 43 to 52.
- Self-Dose administration
- Injection site assessment

  Injection site will be evaluated for ISTR (such as pain, itching, redness and swelling). The injection site will be monitored for any skin irritation within 0.50 and 1.00 hours (within ± 15 minutes) of dosing.

  Note: Photographs will be captured only for subjects who experience ISTR (Injection site reaction). For subjects who experience ISTR, photographs will be captured even if ISTR is resolved earlier.
- Issue of study drugs to the participants for the weeks 44, 45, 46, 47, 48, 49, 50, & 51.
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7), issue of glucometer and / strips for diabetic patients

Weeks 44-51

- Self-Dose administration
- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 to day 7)

Visit 17: Week 52 (End of Treatment or Study Completion for subjects who continue participation)

- Physical examination (DRE may be performed after dosing as per investigator's discretion)
- Weight and BMI (using screening height)
- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature, Respiratory rate)
- Urine drug abuse test
- ECG, Clinical laboratory assessment of Endocrine function, PSA, Biochemistry, Hematology, Urine analysis, Coagulation tests, albumin, SHBG and for diabetic patients-HbA1c
- Testosterone C_{trough} Blood sampling (sampling will be conducted before dose administration) at central lab.
- Recording of Concomitant Medication and AEs, if any
- Diary review for IP accountability and compliance, glucose monitoring (if applicable)
- I-PSS
- Aging Males' Symptoms (AMS) (only to participants aged 40 years or older)
- Patient Global Impression of Change (PGI-C)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Hamilton Depression Rating Scale (HDRS)
- 36-Item Short Form Survey Instrument (SF-36)
- Self-Injection Assessment Questionnaire (SIAQ),
- Assessment of Essential Tasks Questionnaire
- Self-Dose administration
- Injection site assessment

  Injection site will be evaluated for injection site reactions (such as pain, itching, redness and swelling). The injection site will be monitored for any skin irritation after dosing at 0.5 and 1.00 hour (within ± 15 minutes).

  Note: Photographs will be captured only for subjects who experience ISTR (Injection site reaction). For subjects who experience ISTR, photographs will be captured even if ISTR is resolved earlier.

- Glucose monitoring (self-monitoring once weekly) for diabetic patients (between day 2 day 7)
- Continuous Ambulatory Blood Pressure Monitoring (from 0.5 hours pre-dose to 24 hours post-dose)

3.2.1.4 End of Study Safety Follow-up (7-14 days After EOT)

- Recording of Vitals (Pulse rate, Blood pressure, Axillary Body Temperature, Respiratory rate)
- Recording of Concomitant Medication and AEs, if any
- Register completion in IWRS

Reminders to the participants:

Before leaving the site, the participants will be reminded to

- Continue holding off from the use of all prohibited medications.
  e.g., Other T therapy drugs, estrogens or anti-estrogens, long acting opioid analgesics, other androgens (e.g., dehydroepiandrosterone [DHEA]), anabolic steroids, other sex hormones, or other substances/medications, including dietary supplements, known to affect the total testosterone and PK of study drug.
- Participants will be informed by the site team about the next scheduled visit and self-administration schedule and window period for self-administration
- Participants will be asked to inform the site personnel if they experience any discomfort or any other related problems.
- Through text messaging or any other appropriate mode, 12.0 ± 2.0 hours before dosing, participants will be sent reminders prior to each weekly dosing and next scheduled visit.

3.3 Treatment Assignment

A minimum of 80 (for example 80-140) hypogonadal male participants will be enrolled in this study to ensure to complete at least 60-120 participants.

All participants who meet the study eligibility criteria will be assigned study medication to receive Testosterone Cypionate, 75 mg auto-injector, once weekly. The dose will be titrated to 50 mg (if TT Ctrough ≥650 ng/dL) or 100 mg (if TT Ctrough <350 ng/dL) via IWRS. The maximum dose evaluated in the study is 100 mg weekly, and minimal dose is 50 mg weekly. The IMP will be assigned to the eligible participants via IWRS in a single-blind fashion.

Treatment Period: Participants will come to the study site at the scheduled visits and also for PK and Ctrough blood samples.

At week 1: The study medication will be administered by designated clinical study personnel to participants via subcutaneous route.

From week 2 to week 12: Participant will self-administer this study drug from week 2 to week 12. The study medication will be self-administered subcutaneously on the same day of each week and at approximately the same time (7:00 am ± 2 hours) to ensure consistent dosing for PK Analysis.

Dose Titrations at Week 7: Dose adjustment will be made on day 1 of week 7 (visit 4), based upon the week 6 TT (Ctrough value).

Dose titration criteria will be as follows:

- Decrease dose by 25 mg if TT Ctrough ≥650 ng/dL
- Increase dose by 25 mg if TT Ctrough <350 ng/dL
- Maintain dose strength if TT C_{trough} ≥ 350 ng/dL and <650 ng/dL

Note: Additional adjustments to dose will also be made at Weeks 13, 19, and scheduled visits thereafter as necessary based on C_{trough} values measured at week 12, 18, 24, and scheduled visits thereafter, respectively as per "Dose titration criteria".

The treatment doses will be documented separately for each participant for whole treatment duration.

3.3.1 Participant Identification

Participants will be assigned a sequential screening number (including site number) during screening visit. The screening number is a unique identification code consisting of a three-digit site code followed by a three-digit participant identifier (e.g., first site first screening number of participant: 101-001). The screening number will be sequentially assigned at each site level. At the start of the treatment period (week 1), after confirming that the participant fulfils the inclusion and exclusion criteria, the participants will be given a study participation number via IWRS. Please note that the study participation number is a unique four-digit system-generated number that will be assigned to the individual eligible participant. To protect the participant 's identity, participant initials and participant number will be assigned by the Investigator to each study participant and used in place of the participant 's name when the Investigator reports AEs and/or other study-related data. Personal information will be treated as confidential but may need to be reviewed by authorized

representatives of the Sponsor (monitor and auditor, respectively) and regulatory authorities. The participant 's consent or direct access to his original medical records for data verification purposes must be obtained prior to their participation in the study.

The shipments, dispensing, compliance verification, reconciliation and return of IMP will be handled by the site team of pharmacist or investigator designated personnel. The study pharmacist/designee will be delegated the responsibility of administering or supervising the on-site administration of IMP. The delegation of this activity will be recorded on the Responsibility Delegation log at the site.

Blinding

As this study is a single-blind (with respect to dosage strength) study, the study participants who self-administer the study drug, and the clinical staff responsible for conducting study assessments will remain blinded (at the PI's discretion) to the assigned dosage strength especially from first titration of dose i.e. at week 7 in order to minimize assessment, observation, and reporting bias.

Throughout the study, the PI and additional staff member (at the PI's discretion) will remain unblinded to the testosterone cypionate dosage for the participant safety monitoring and dosage adjustment purposes based on periodic serum total testosterone levels, as applicable. Individuals at the Clinical Laboratory, Bioanalytical and Clinical Data Management vendors who receive and/or manage study data will remain unblinded.

Unblinding

As this is a single-blind study where study participants, and the clinical staff responsible for conducting study assessments will remain blinded (at the PI's discretion) to the assigned dosage strength in order to minimize assessment, observation, and reporting bias. PI and additional staff member (at the PI's discretion) will remain unblinded to the testosterone cypionate dosage for the participant safety monitoring and dosage adjustment purposes based on periodic serum total testosterone levels, as applicable. There are instances where unblinding of blinded study personnel or participants may be required; however, these instances are rare and will be permitted only in the event of a medical emergency or other circumstance where knowledge of the assigned dose strength is considered essential for the appropriate clinical management of the participant. Any such unblinding will be documented, including the reason, date, personnel involved, and impact on study conduct, if any.

Routine study assessments, data review, and study evaluations by blinded clinical staff where applicable will continue to be performed without access to dosage allocation information and until such time that all discrepancies in the clinical database are resolved (i.e., at the time of the database lock)

In the unlikely event where unblinding is required, the date and time when the Investigator removed the study blind for an individual participant will be documented by the IWRS.

3.4 Investigational Product Management

3.4.1 Study Medication (Investigational Product) Description

This study will involve one investigational product of Amneal Pharmaceuticals, LLC.

Investigational Drug Product	Testosterone Cypionate auto-injector for subcutaneous use **Manufactured by:** Amneal Pharmaceuticals, LLC. **Dosage form and Strength:** 50 mg, 75 mg, 100 mg weekly subcutaneous injection via autoinjector

IMP will be shipped to the site by the Clinical Trial Supplies management vendor. The sponsor will outsource the activities to CRO who in turn will coordinate CRO's Logistics team or with approved qualified vendors for shipment of study medication to the study sites.

3.4.2 Study Medication Packaging and Label

The Amneal's test product i.e. study IMP, Testosterone Autoinjector (50 mg, 75 mg & 100 mg), will be imported by the Sponsor/ designee and stored at the Clinical Trial Supplies management vendor till shipment to site. All import and logistics activities including packaging and labelling will be managed by CRO / approved vendor.

Packaging and Labelling:

The IMP (outer carton and pouch) will be packaged and labeled per Good Manufacturing Practice (GMP) labeling requirements. The information on the label will include, at a minimum, the following:

- Name of the sponsor
- Protocol No./Study code
- Name of the IMP

- Route of administration
- "For Clinical Trial Use Only"
- Storage conditions
- Participant number
- Site ID

The investigational product will be packaged per Good Manufacturing Practice (GMP) and the labelling process will be performed by designee site personnel (unblinded) as described in Section 3.4. The information on the product label will include the following at a minimum:

- Protocol No./Study code
- Name of the IMP
- Route of administration
- "For Clinical Trial Use Only"
- Storage conditions
- Participant number

Caution should be taken not to identify the strength on the label for the IMPs/IPs which are dispensed and to be administered for the participants in order to maintain blinding procedure (e.g. dosage strength or dose not to be mentioned on the label), and complete details to be covered in the IMP handling manual.

3.4.3 Investigational Product Storage Conditions

The IMP should be stored at room temperature [68°F to 77°F (20°C to 25°C)] in a locked storage facility to which only the authorized study site personnel will have access. Temperature should be controlled and documented once daily on working days. Protect from light (keep in carton until time of use).

If there are excursions in temperature outside the given range, site staff should contact and inform the CRO within 1 (one) business day of becoming aware of the issue. The sponsor will be responsible for the final release or rejection of the affected IMP.

Transit temperatures during shipping will be monitored using temperature data loggers, and storage temperature at the site will be monitored per the site's standard operating procedures (SOPs) or study specific IMP handling manual.

Once the dispended IMPs is issued to the participant, the site staff should instruct the participant to store at

room temperature until it is self-administered or returned to site staff.

3.4.4 Study Medication Accountability

The IMP will be supplied to the site only after approval for the study is received from the ethics committee and competent regulatory authority (as applicable). Accurate written documentation of all drug transfer processes between the Sponsor, central depot, the site, and the participants will be maintained. An automatic trigger will generate an IMP re-supply order in the interactive web response system (IWRS) if the minimum site stock threshold is reached.

The quantity of the IMP and the date it is delivered to the site, the quantity of IMP and the date it is dispensed to the participants and then returned to the site must be documented. Moreover, the quantity of unused IMP must be accurately documented at the end of the study (drug inventory records, drug return and reconciliation records).

The documentation should be filed in the investigator's file. The IMP accountability records will include:

- Confirmation of IMP delivery to the trial site
- The inventory of IMP received at the site
- The amount of IMP retained for each shipment
- The amount of IMP dispensed to each participant
- The use of IMP by each participant
- The return of used and unused IMP by each participant for the total treatment period
- The return of used and unused IMP to the Sponsor or the designee (as per IMP handling-related manual / plans)
- The details of the IMP such as dates, quantities, batch numbers and participant numbers should be recorded in all the above accountability documents.
- The seal for protection on the IMP pack should remain intact until ready for use by the participant at the treatment visits.

3.4.5 Potentially Malfunctioned IMP

All malfunctioned, used and unused IMP, as well as unused study supplies, will be stored under appropriate temperature and storage conditions and returned as per procedures explained to the clinical sites. These IMPs

may be further analyzed for regulatory purposes. Separate documentation may be provided with details of the analysis of returned IMPs.

Participants should be instructed to contact site in case of malfunctioned IMP, the site may instruct the participant to self-administer any of the doses available immediately for appropriate action for the malfunctioned IMP e.g., replacement with new IMP.

3.4.6 Handling of Retention Samples

After receiving the investigational drug products, a minimum quantity of 30 units in the original container should be retained from each shipment as per random selection method and the remaining Investigational drug products shall be used to conduct the study. In case of multiple shipments, at least 1 unit per each shipment in the original container must be retained at each site. The retention samples will be stored under appropriate conditions at the site as per the written instructions provided.

Retention samples will be kept for at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least 5 years following the date of completion of the study in which the retained sample was obtained.

In addition, the investigators should follow the procedures of 21 CFR 58 and current ICH E6, "Good Clinical Practice: Consolidated Guideline," for retention of study records and data to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Instructions to be provided to sites will be captured in a separate retention plan.

4. Participant Selection and Withdrawal Criteria

4.1 Selection of Study Population

A minimum of 80 (example 80-140) eligible participants will be enrolled in the study to ensure completion of 60-120 Hypogonadal male participants in this study from approximately 3-10 sites in the US. Participants will be assigned to study medication only if they meet all the inclusion criteria and none of the exclusion criteria. Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study and participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Each participant is expected to be in the study for up to 58 weeks, including an approximately 4-week screening period, a 24-week primary treatment and evaluation period, continued treatment with ongoing safety assessment beyond Week 24, and a follow-up visit conducted 7 to 14 days after the last dose.

Participants who have been dosed with at least 1 dose of IMP/ study drug and then discontinues for any reason will not be replaced; however, allowance for automatic replacement will be made if a participant withdraws/discontinues but prior to dosing of first dose of IMP/ study drug.
A participant may be rescreened once, at the discretion of the Investigator. Prior to performing any rescreening procedures, a new informed consent must be obtained from the participant. A new screening number will be assigned to the participant as per section 3.3.1.

4.1.1 Inclusion Criteria

Each participant must meet all the following criteria to be enrolled in this study:

1. Confirmation of Hypogonadism Before Initiation of Investigational Product:
   Ensure presence of at least one sign or symptom that may be related to low testosterone values and is/are consistent with hypogonadism which may include the following:
   - Decreased sexual desire
   - Decreased energy
   - Decreased facial or body hair
   - Loss of muscle mass and bone density

- Erectile dysfunction
- Low sperm count
- Depressed mood
- Lethargy
- Sleep disturbances
- Anemia
- Changes in cholesterol levels
- Mood changes
- Irritability
- Fatigue
- Increase in body fat
- Difficulty with concentration and memory
- Decrease in endurance

Prior to initiating investigational product administration (study drug), the diagnosis of hypogonadism should be confirmed by ensuring that serum Total Testosterone concentrations have been measured in the morning on at least two separate days at least 72 hours apart during the screening period and that these serum Total Testosterone concentrations should be as detailed below:

2. Participants with fasting morning total serum testosterone levels (measured on two separate days) should be < 300 ng/dL.
3. Qualifying total serum Testosterone concentrations (T) will be obtained on 2 separate occasions at least 72 hours apart during screening period.

   One repeat total T concentration will be allowed if 1 of the 2 morning total T concentrations is ≥300 ng/dL. After retesting, if 2 of the 3 TT concentrations are <300 ng/dL, the participant will be eligible to participate in the study.

   The first total Testosterone (TT) concentration will be obtained after completion of washout from current Testosterone (T) therapy, if applicable.
4. Prostate specific antigen (PSA) between 0-2.5 ng/mL for subjects ≤ 50 years of age and between 0-4 ng/mL for subjects > 50 years of age will be confirmed during screening.

5. Males (by birth) of 18 to 75 years of age with a documented diagnosis of hypogonadism having BMI range of 18.5 to 39.9 kg/m^2.
6. All participants will be required to agree to practice effective contraception throughout the duration of the study and for 30 days after receiving the last dose of testosterone. Acceptable methods of birth control included condom with spermicide, vasectomy, or monogamous relations with a female partner who are non-childbearing potential (post- menopausal, surgical or congenital sterility) or is of child-bearing potential and practiced a reliable method of contraception (hormonal contraception, double-barrier methods with spermicide, or intrauterine device).
7. Low-density lipoprotein cholesterol < 190 mg/dL.
8. Willing to give their written informed consent to participate in the study, able and willing to comply with all study procedures, including being available for all study Visits.
9. Adequate venous access to allow collection of a number of blood samples via a venous cannula.
10. Participants without prior TRT use required to have haemoglobin (Hb) ⩽ 16 g/dL at baseline or should have Hb of ⩽17 g/dL for participants with TRT use within 30 days prior to screening.
11. Participants with diabetes mellitus may be enrolled, provided they have been on a stable dose and regimen of anti-diabetic medication(s) for at least 4 weeks prior to screening and have a HbA1c level ≤ 9.0%, or are considered adequately controlled at the discretion of the PI.
12. Participants with dyslipidaemia (hyperlipidaemia) may be enrolled, provided they have been on a stable dose and regimen of lipid-lowering medication(s) for at least 4 weeks prior to screening or are considered adequately controlled at the discretion of the PI.
13. Based on measurement of BP in the clinical site (using the cuff method), participants with hypertension (SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg) may be enrolled, provided they have been on a stable dose and regimen of antihypertensive medication(s) for at least 1 month prior to screening or are considered adequately controlled at the discretion of the PI.

    or

    Based on measurement of BP in the clinical site (using the cuff method), participants who are normotensive (SBP < 140 mm Hg and/or DBP < 90 mm Hg) and not receiving antihypertensive medication are also eligible for enrolment.

4.1.2 Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study:

1. Individuals who have an allergic reaction or idiosyncratic reaction to cotton seed oil.
2. Current opioid use
3. History of intolerance, allergy, or idiosyncratic reaction to testosterone products.
4. Body mass index (BMI) >40.0 kg/m^2.
5. Hematocrit ≥ 52% at the initial Screening Visit.
6. Individual history or current evidence of prostate cancer.
7. Men with two (2) total testosterone levels below 100 ng/dL during the screening period.
8. Abnormal ECG considered clinically significant by investigator at Screening.

   Or

   History of long QT syndrome or unexplained sudden death in a first-degree relative (parent, sibling, or child).
9. Any malignancy diagnosed or treated within 5 years of the date of Screening with the exception of non-melanoma carcinoma of the skin.
10. Presence of prostate nodule or induration upon digital rectal exam (DRE).
11. Obstructive uropathy of prostatic origin and of a severity that, in the opinion of the Investigator, contraindicated the use of T therapy and/ or participants with lower urinary tract symptoms (LUTS), as indicated by an International Prostate Symptom Score (I-PSS) greater than 19.
12. Participants with New York Heart Association Class III or IV congestive heart failure prior to Visit 1.
13. Myocardial infarction, unstable angina leading to hospitalization, percutaneous coronary intervention, coronary artery bypass graft, uncontrolled cardiac arrhythmia, stroke, transient ischemia attack, carotid revascularization, endovascular procedure, or surgical intervention for peripheral vascular disease within 6 months prior to Visit 1 (Screening).
14. History or current treatment for thromboembolic disease or hypercoagulatory condition, or use of anti-thromboembolic medications. Use of low-dose aspirin (81 mg) will be permitted.
15. Participants using systemic adrenocorticotropic hormone or oral or depot corticosteroids. Inhaled corticosteroids for respiratory conditions are permissible.

16. Untreated sleep apnea.

17. Historical or current evidence of any clinically significant disease or disorder that, in the opinion of the Investigator, may have caused participation in the study to be detrimental to the participant or which may affect the results of the study. This included cardiovascular, renal, hepatic, hematological, neuropsychological, endocrine, gastrointestinal, and pulmonary disease.

    Subjects with an endocrine disorder requiring treatment other than hypogonadism must be on a stable dose of replacement medication for at least 3 months prior to study entry.

18. Positive serology for human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (HCVAb) at the Screening Visit.
19. History of drug or alcohol abuse within the past 2 years that in the opinion of the investigator could interfere with study participation and/or influence study efficacy and safety endpoints assessments.
20. A positive drug screen without documentation of a prescription and medical condition requiring treatment with the drug for which the screen was positive. Exception for tetrahydrocannabinol will be allowed in states where recreational use of marijuana is legal.
21. Clinically significant history tobacco or cigarette consumption as per the Investigator's discretion within 2 years of study period dosing. Light smokers (≤5 cigarettes per day) are allowed to take part in this study.
22. Participants with active suicidal ideation with method, intent, or plan (C-SSRS Categories 3, 4, or 5) during the last 6 months prior to screening.
23. Any history of a suicide attempt (C-SSRS Category 9) during the last 12 months prior to screening.
24. Any patient exhibiting new-onset or worsening depression, anxiety, or suicidal thoughts (Categories 1-2) during the last 6 months prior to screening.
25. Any skin condition that could confound injection site assessments (e.g., dermatographism, urticaria, or atopic dermatitis, tattoos, scarring, psoriasis, etc.) at the injection site.
26. Participants with history and current diagnosis of deep veinous thrombosis (DVT), pulmonary embolism (PE), or known thrombophilia.
27. Use of any drug that could interfere with measurement or assessment of serum androgen levels, including 5 alpha-reductase inhibitors, anabolic steroids, and drugs with anti-androgenic properties (e.g., spironolactone, cimetidine, flutamide, bicalutamide, and ketoconazole). These drugs must be stopped for

at least 1 month prior to study entry (6 months in the case of dutasteride). Patients taking potent, short or long- acting opiate therapy on a daily basis are not eligible for the study.

28. Use of over-the-counter products (OTC) including natural health products (e.g., food supplements and herbal supplements such as saw palmetto or phytoestrogens) that may affect total T levels, within 7 days prior to study entry.
29. Participants who use clomiphene, enclomiphene or OTC androgenic steroid derivatives including investigation and drug products that may affect reproductive potential, or have been treated with such products in the past 6 months prior to screening (visit 1).
30. Exclude the following potential participants:
    a) Known history of polycythemia vera or secondary polycythemia, such as polycythemia due to untreated sleep apnea or severe chronic obstructive pulmonary disease (COPD).
    b) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than 3 times the upper limit of normal (ULN).
    c) Tattoo removal in the region of the study drug application within six months of screening (visit 1).
    d) Chronic kidney disease documented by an eGFR less than 30 mL/min calculated by CKD-EPI formula.
    e) History of use of an anti-estrogen treatment within 90 days prior to screening.
    f) Participants taking any high-potency opioids (e.g., oxycodone, hydrocodone, etc.) or glucocorticoids > 7.5 mg prednisone equivalents per day (e.g., hydrocortisone 30 mg, methylprednisolone 6 mg or dexamethasone 1.2 mg) within 1 week before the screening visit, except men who are taking these medications for a chronic condition and are anticipated to continue treatment. Inhaled corticosteroids for respiratory conditions are permissible.
31. Participants who are currently using 5-alpha reductase inhibitors (e.g., finasteride, dutasteride)
32. Administration of any other investigational compound within 1 month prior to Screening or 5 half-lives of the Testosterone (whichever was longer).
33. Within 12 months of the Screening Visit, the participant have taken estrogen, gonadotropin-releasing hormone agonists, or growth hormone or anti-androgens.
34. Participants who have taken, long-acting opioid analgesics in last 1 month prior to study visit 2.

35. Participants who have taken other androgens (e.g., dehydroepiandrosterone [DHEA]), anabolic steroids, other sex hormones, or other substances/medications, including dietary supplements, known to affect the PK of study drug.
    a) Discontinuation of these substances/medications will be allowed at the initial Screening Visit provided that the half-life of the substance/medication allowed complete washout (minimum of 5 half-lives) during the washout section of the Screening Phase. Washout must be completed before the Qualification (Qual) Visit.
    b) DHEA will be required to be washed out for a minimum of 4 weeks.
    c) Participants who require the use of these substances/medications during the duration of the study will be excluded.
36. Concurrent treatment with medications that may impact the absorption, distribution, metabolism, or excretion of study drug or place the participant at risk for treatment with T.
37. Participant has a partner who is planning pregnancy during the course of the study.
38. Treatment with any other investigational drug within 30 days of study entry or ≥ 5 half- lives (whichever is longer) and at any time during the study.
39. History of noncompliance to medical regimens or potential unreliability in the opinion of the investigator.
40. Onset of gynecomastia within the previous 6 months.
41. Participants who will be considering or have scheduled any major surgical or dental procedure anticipated to be associated with significant blood loss (≥500 mL) during the study.
42. Participants who donated plasma or blood within 56 days of the Screening Visit or had a history of donation of more than 500 mL of blood or plasma within 3 months of Screening. Blood and plasma donation will be prohibited further during the duration of the study.
43. Unable to understand verbal or written English or any other language in which a certified translation of the informed consent is available.
44. If, for any reason, the investigator believes that the participant is not a viable candidate to receive the study drug.

4.1.3 Enrolment Criteria for Treatment Initiation

Each participant in this study must meet all the following criteria at screening:

- Adult male with a confirmed diagnosis of Hypogonadism containing consistent signs and symptoms of androgen deficiency and documented low testosterone concentration (< 300 ng/dL).
- Any of the following treatment regimens prior to screening Visit are acceptable:
    - Treatment-naïve (participants who have never received any form of testosterone replacement)
    - Currently treated with oral buccal, or transdermal testosterone regimen (participants will undergo 2-week washout prior to visit 1).
    - Currently treated with a stable IM testosterone regimen (dose and interval) for a minimum of 3 consecutive doses (dose must be 50 mg to 400 mg administered at intervals no greater than every 4 weeks) (participants will undergo 5-week washout prior to visit 1); or
    - Completed washout of treatment prior to screening (i.e., 2-week washout for buccal or transdermal, or 5-week washout of IM testosterone or end of dosing interval for Testopel participants i.e. at least 12-weeks from the initiation, prior to visit 1). Participants who have completed washout of treatment prior to screening will follow the same procedures as participants who are treatment-naïve.
- Qualifying Testosterone concentrations, obtained during screening/qualification visits as follows:
    - Treatment-naïve participants, or participants on current testosterone therapy who have completed above defined minimum washout period must have 2 fasting morning TT concentrations <300 ng/dL during the screening period. Qualifying total Testosterone concentrations will be obtained between 07:30 AM - 10:00 AM on two separate occasions at least 72 hours apart during screening period.
    - Participants who have 1 sample >300 ng/dL may have 1 retest for TT concentrations (Visit 1c) which must occur no less than 7 days after the previous test. After retesting, if 2 of the 3 TT concentrations are <300 ng/dL, the participant will be eligible to participate in the study.

4.2 Withdrawal/Discontinuation of Participants from Study Medication and/or the Study

If any of the criteria listed below are met, Testosterone Cypionate auto-injector for subcutaneous use will be stopped and the participant will be withdrawn from the study:

1. Increase in baseline (visit 2) PSA ≥1.4 ng/mL from the screening PSA value.
2. Elevated hematocrit >55% during the primary evaluation phase or Continued Safety Follow Up (Beyond

Week 24) of the study.

3. Intermittent disease or condition that (e.g. participant exhibiting new-onset or worsening depression, anxiety, or suicidal thoughts (Categories 1-2 of C-SSRS)), in the opinion of the investigator, might compromise the participant's continued safety or eligibility for the study i.e., Occurrence of any of the following cardiovascular events: myocardial infarction, new onset angina, unstable angina, cardiac revascularization (bypass, stenting, or endarterectomy), transient ischemic attack, or cerebrovascular accident.
4. Anaphylaxis.
5. Participants receiving Testosterone 50 mg who required a dose reduction and who had a total T C_{trough} ≥650 ng/dL.

   Or

   Participants receiving Testosterone 100 mg who required a dose increment and who had a total T C_{trough} <350 ng/dL.
6. During the first 12-week Treatment phase, if the subject / participant misses more than 1 dose, that specific subject / participant will be excluded from the efficacy analysis.
7. Adverse events for which, in the opinion of the investigator, continued study medication or maintenance would be detrimental.
8. Administrative reasons (non-compliant, uncooperative etc.)
9. Participant decision not to participate further in the study (Withdrawal of informed consent).
10. If it is in the participant's best interest, based on decision of the Principal Investigator or Medical Sub-Investigator
11. Lost to follow-up.
12. Discontinuation of the study for any reason by the investigator, regulatory authorities, institutional review board/ethics committee, Amneal Pharmaceuticals, LLC., clinical/ contract research organization (CRO), or Medical Monitor.

4.2.1 Withdrawal of Participants from Follow-up/ Lost to follow-up:

Participants may voluntarily withdraw their participation from the study at any time without having to provide a reason or a participant may be withdrawn from follow-up at the Investigator's discretion if it is in the participant's best interest. The reason(s), including the primary reason for withdrawal from follow-up, if

provided by the participant, will be recorded in the eCRF. Although a participant is not obliged to give his reason(s) for discontinuing study participation prematurely, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the participant 's rights. If the participant does not wish to provide a reason, the source documents and the eCRF should document the reason for discontinuation as "withdrawal by participant". Whenever possible, the Investigator should request the participant to return for a clinic assessment at the time of or soon after discontinuation from follow-up. The Investigator is required to make every effort possible to follow the participant concerned for survival and hospitalisation after discontinuation of follow-up on the condition that the participant has not withdrawn consent to do so.

If participants refuse to return to the outpatient clinic for the scheduled visits, all reasonable efforts should be made to contact the participant by telephone at the time point of the scheduled visits. In such situations and unless the participant withdraws informed consent for further participation in the trial, all participants who withdraw from follow-up visits prematurely will continue to be followed for the occurrence events suggestive of the study outcomes.

It is vital to obtain follow-up data on any participant withdrawn because of an AE. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures. If a participant is discontinued due to an AE, the event should be followed by the Investigator through contact with the participant until resolution or stabilisation has occurred. All AEs should be followed until resolution, stabilisation or the participant is lost to follow-up and cannot be contacted. Reasons for discontinuations will be documented in the eCRFs. Participants who discontinue prematurely will not be replaced.

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study, the study site must have "due diligence" by documenting in the source documents steps taken to contact the participant, e.g., dates of telephone calls, registered letters, etc. A participant should not be considered lost to follow-up until due diligence has been completed or until the end of the study.

4.2.2 Handling of Withdrawals

If a participant discontinues from the study for any reason after taking at least one dose of IMP, and before End of the treatment (EOT), then the participant will be encouraged to return to the study site for an end of study safety follow-up visit. In addition, the safety follow-up and all other applicable procedures outlined in

17.1 “Table of Study Assessment and Schedule of Events”.

When a participant withdraws from the study, the reason(s) for withdrawal must be recorded in the participant’s source documents and electronic case report form (eCRF). The investigator should make a reasonable effort to ascertain the reason while fully respecting the participant’s rights, request that the participant return all study medication and request that the participant return for a final visit, and subsequently follow-up with the participant on any unresolved AE. It is vital to obtain follow-up data on any participant withdrawn because of an AE. In every case, efforts must be made to undertake protocol-specified safety follow-up procedures.

5. Treatment of Participants

5.1 Treatment

The Amneal's investigational product i.e., study drug, Testosterone Cypionate (50 mg, 75 mg & 100 mg) Auto-injector (for both the Treatment Phase and Continued Safety Follow Up (Beyond Week 24)) will be supplied by Amneal or its designee.

5.1.1 Study Drug and Administration Schedule

The following treatments will be administered during the study:

All participants who meet the study eligibility criteria will be assigned to receive Testosterone Cypionate auto-injector, 75 mg. The study medication will be administered by designated clinical study personnel at week 1 to participants via subcutaneous route weekly once, on the same day of the week and at approximately the same time (7:00 am ±2 hours) through the duration of the study (self-administered by participant from week-2 onwards). Adjustments to dose will be made at Week 7 based upon the Week 6 blood concentration (C_{trough}) value. Dose titration criteria will be as follows:

- Decrease dose by 25 mg if Testosterone $C_{trough} \geq 650$ ng/dL
- Increase dose by 25 mg if Testosterone $C_{trough} < 350$ ng/dL
- Maintain dose strength if Testosterone $C_{trough} \geq 350$ ng/dL and < 650 ng/dL

Note: Additional adjustments to dose will also be made at Weeks 13, 19, and scheduled visits thereafter as necessary.

ADMINISTRATION SCHEDULE

- At week 1: The study medication will be administered by designated study personnel to participants via subcutaneous route.
- From week 2 to week 12: Participant will self-administer this study drug from week 2 to week 12. The study medication will be self-administered subcutaneously on the same day of each week and at approximately the same time (7:00 am ± 2hrs) to ensure consistent dosing for PK Analysis.
- Participants will also self-administer the study medication as directed though the duration of the study.
- The pharmacist (or designee) will issue the dispensed IMPs at appropriate periods and retrieve the used study medication auto-injectors from the participants.

Administration Procedure:

Participants will receive or self-administer a Subcutaneous injection of Testosterone Cypionate Auto-Injector, each week (Q7d), at ambient temperature during morning hours.

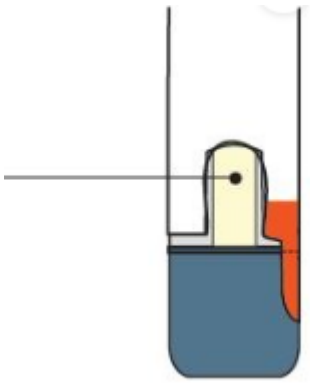
Prior to Dosing:

Prior to administration of the Subcutaneous injection, the location of the injection site must be identified, fixed.

Drug products shall be inspected visually for particulate matter and discoloration prior to and during administration.

Instructions for Auto-Injector:

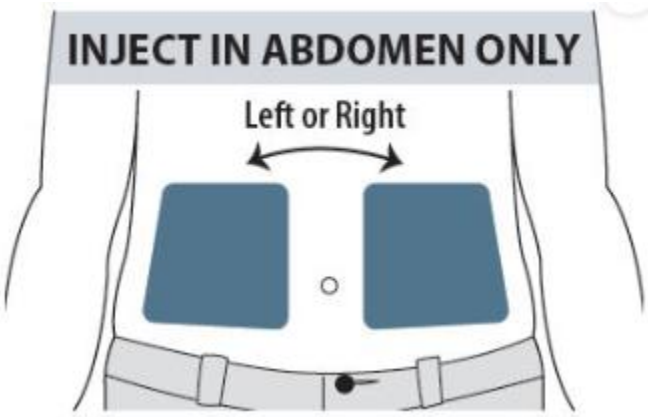
- Do not remove Cap until ready to inject.
- Inspect Auto-Injector for any visible damage. Do not use if it appears damaged or broken.
- Check the expiration date. Do not use if the expiration date has passed.
- Inspect the medicine through the Viewing Window; it should be clear to light yellow and free of visible particles see below figure:



Do not use if the medicine is cloudy or if visible particles are present. Do not use the Test Product if the seal is broken. You may notice an air bubble, this is normal.

Selection & Preparation Injection Site:

- Wipe the abdomen injection site with an alcohol swab.
- Only use the left or right side of the abdomen (belly) for injection sites. (Consecutive week dose should be administered to contralateral side and should be different from a previous site).
- Do not use the area within 2 inches around your umbilicus (belly button) see below figure.

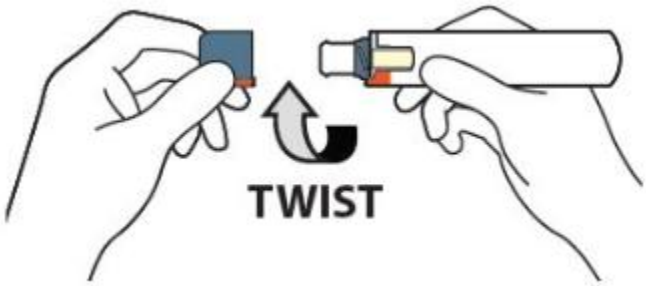


- Do not use in areas where the skin is tender, bruised, red, scaly, or hard. Avoid areas with scars, tattoos, or stretch marks.

Administration procedure:

Remove Cap:

- Twist the Cap to remove (this will also break the red safety seal). See below Figure:

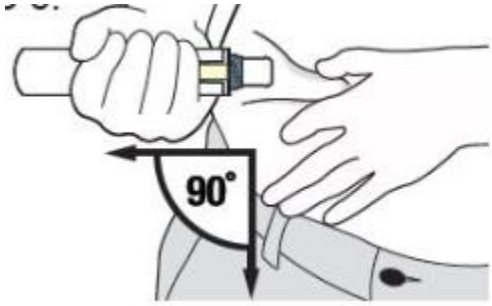


- After the Cap is removed, a few drops of liquid may appear, this is normal.
- The Auto-Injector should be used or discarded after the Cap is removed.
- Do not re-Cap for later use.
- Do not touch the Needle End of the Auto-Injector with your hand or fingers after the Cap is removed, doing so can cause injection and injury to your hands.

Position Auto-Injector:

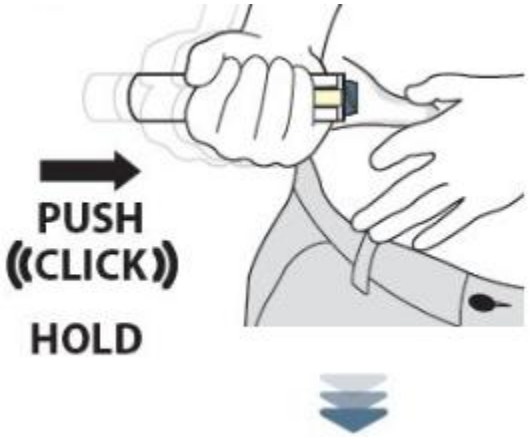
- Gently squeeze the abdomen injection site to create a raised area and hold that area firmly until after the injection is complete see below Figure.

- Place the Needle End of the Auto-Injector on the abdomen injection site
- Keep the Auto-Injector straight at a 90 degree angle to the abdomen injection site. see below Figure.

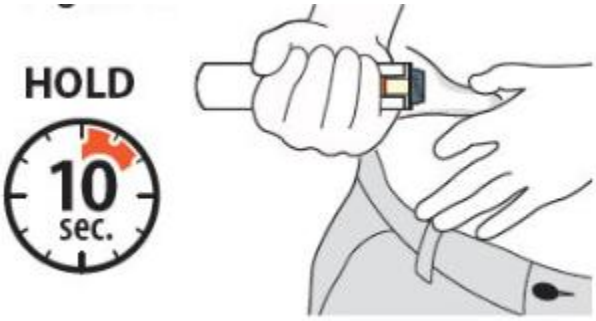


Inject & Hold Down:

- Firmly push the Auto-Injector down on the abdomen site and continue to hold down after you hear the "CLICK" see below Figure.



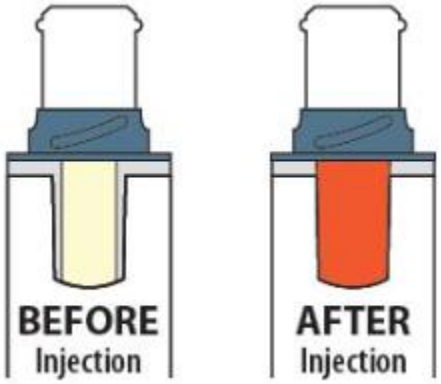
- While holding the Auto-Injector down, slowly count from 1 to 10 to allow all of the medicine to be delivered see below Figure.



- Keep holding the Auto-Injector down for a total of 10 seconds even if your injection is complete and the viewing window turns orange sooner.
- It is normal if there is slight bleeding from the site after injection. If this occurs, hold a cotton ball or gauze on the area for a few seconds. Do not rub the area.

Inspect Viewing Window:

- After injecting, inspect the Viewing Window. It should be orange, confirming the dose was administered see below Figure.



- If the Viewing Window is not orange:
- Do not use another Auto-Injector.
- Do not attempt another injection.

5.1.2 Study Restrictions

1. Participants should refrain from using any medicines which are restricted within 14 days prior to week 1 study drug administration and will be instructed to refrain from the same till the duration of the study.
2. Blood or sperm donations during the study period.
3. Having Tattoos on any body part during the study period.

5.1.3 Treatment Compliance

Participant compliance will be assessed at each scheduled study visit for the auto-injector study medication. During the treatment phase and continued safety follow-up, participants will attend study visits at scheduled dosing intervals in accordance with the protocol.

The study medication will be administered by designated clinical study personnel at week 1 to participants via subcutaneous route, and participant will self-administer the rest of the once weekly doses via SC route on the same day of the week and at approximately the same time (7:00 am ±2 hours) to ensure consistent dosing for PK Analysis. Therefore, IMP compliance of the study treatment will be monitored and documented.

Note: *IMP compliance (%) = (Number of doses taken/Number of planned doses per the dosing schedule) × 100.*

The accepted Full PK population used for pivotal efficacy evaluation includes each subject who meets all the inclusion/exclusion criteria, administers a prespecified proportion of the scheduled doses (e.g., not less than 85% primarily in the treatment phase- first 12 weeks) of the assigned product for the specified study duration, does not miss the scheduled dosing for more than 1 dose, and completes the study with no protocol violations that would affect the treatment evaluation or primary outcome of the study.

5.1.4 Handling of Autoinjector Complaints

If the participant suspects that an auto-injector is not working properly, the participant should immediately contact study site personnel to get it replaced with a new autoinjector. All auto-injectors suspected of not working properly will be sent to Amneal for further evaluation.

5.1.5 Overdose Management

An overdose is any dose of study medication given to a participant or taken by a participant that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported. Overdoses without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these will be reported on the relevant AE or SAE sections, as applicable, in the eCRF.

6. Assessments of Efficacy and Related Parameters

Before performing any study procedures, all potential participants will sign an informed consent form/document (ICF). Participants will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the participant. The investigator or designee will also sign the ICF.

As shown in Appendix 17.1 (Schedule of Assessments), participants will undergo screening evaluations, initiate treatment at Week 1 (Day 1), and complete a 24-week primary treatment and evaluation period, with continued participation thereafter for ongoing safety assessment.

At Week 1, 6 and/ or Week 12 participants will be evaluated for PK analysis up to 168 hours. Each participant will undergo post treatment safety follow-up at 1-2 weeks after the last dose of treatment.

6.1 Medical History

A complete medical history including hypogonadism and hypogonadism medication history will be obtained at screening. This will include a review of all current and past conditions, procedures and surgeries. Current medications and any medications taken at least during the past 12 weeks will be recorded.

6.2 Demography

Demographic characteristics such as date of birth, gender (male), age, race, ethnicity, height and weight and BMI will be recorded at screening.

6.3 Assessment of Pharmacokinetic Parameters (C_{max}, $AUC_{0\text{-}168\ h}$, C_{trough}, and C_{avg})

Once the participants are enrolled and assigned to treatment at week 1, blood sampling will be conducted at week 1 and 6 for up to 168 hours for PK analysis estimation of TT, DHT, DHTC, E2 and Testosterone Cypionate to obtain baseline values for 45 participants and also at week 12 to assess safety and efficacy for all participants.

A maximum of 39 Blood samples for PK characterization will be obtained at below scheduled times.

PK samples for 45 participants at week 1, week 6 and week 12 and details are as follows		
Week	No. of Samples	Sampling schedule
1 (full PK)	10	0.00 (pre-dose sample), 0.50, 3.00, 6.00, 9.00, 12.00, 24.00, 48.00, 72.00, and 168.00* hours post-dose in plain vacutainers. *:Corresponds to Day 1 of Week 2.
6 (full PK)	11	0.00 (pre-dose sample), 0.50, 3.00, 6.00, 9.00, 12.00, 24.00, 48.00, 72.00, 144.00, and 168.00* hours post-dose in plain vacutainers. *:Corresponds to Day 1 of Week 7
12 (pivotal-full PK)	13	0.00 (pre-dose sample), 3.00, 6.00, 9.00, 12.00, 24.00, 36.00, 48.00, 72.00, 96.00, 120.00, 144.00, and 168.00* hours post-dose in plain vacutainers. *: Corresponds to Day 1 of Week 13
4, 5, 9, 10 and 11 (steady-state)	5	Before dose administration

PK sampling will be performed at week 12 for all participants and details are as follows.		
Week	No. of Samples	Sampling schedule
1, 4, 5, 6, 9, 10 and 11 (Pre-dose / steady-state)	7	Before dose administration
12 (full PK)	13	0.00 (pre-dose sample), 3.00, 6.00, 9.00, 12.00, 24.00, 36.00, 48.00, 72.00, 96.00, 120.00, 144.00, and 168.00* hours post-dose in plain vacutainers. *:Corresponds to Day 1 of Week 13

To ensure compliance with overnight fasting requirements, subjects may be housed at the clinical site when appropriate facilities are available. For clinical sites that do not have the infrastructure to accommodate overnight stays, subjects may instead return to their homes and are instructed to maintain the required fasting conditions until they return to the site the following day for scheduled study procedures and /or PK sample blood sample collection. Upon arrival at the clinical site the next day, subjects will provide written confirmation that they adhered to the fasting requirements as instructed.

Note: The 168-hour post-dose sample of week 1 dose corresponds to Day 8 of Week 1 (day 1 of week 2), the

168-hour post-dose sample of week 6 dose corresponds to Day 8 of Week 6 (day 1 of week 7), and the 168-hour post-dose sample of week 12 dose corresponds to Day 8 of Week 12 visit (day 1 of week 13) it should be collected prior to dosing on that day.

C_{trough} samples: For dose titration, Trough TT blood samples will be obtained within 15 minutes before dose administration on Day 1 of week 6 (visit 3), week 12 (visit 5), week 18 (visit 7), week 24 (visit 9), and scheduled visits thereafter for all participants.

The acceptable window period of -15 (fifteen) minutes for 0.00 hours pre-dose samples.

The acceptable window for in-house PK sampling time points is ± 5 minutes, and ± 2 hours for ambulatory PK blood samples.

At week 1, since testosterone is an endogenous substance, the serum concentration of testosterone should be corrected for baseline endogenous levels by subtracting pre-dose 0.00 hours baseline value. Any negative value obtained from baseline correction should be designated as zero. For week 6 and week 12 PK profiles, baseline correction is not necessary.

In-house blood samples may be collected through intravenous cannula or by direct vein puncture as per site procedures.

To ensure the patency of intravenous cannula where applicable, 0.5 mL of normal saline will be injected into the cannula after each sample withdrawal and each time before sample collection 0.5 mL of saline mixed blood sample will be discarded.

If the blood sample collection time coincides with the other study events like vitals and meal, the sequence of the events to be followed as blood sample collection followed by vitals and meal.

Note:

The additional (maximum of 9) samples for serum TT will also be collected along with clinical laboratory assessments at selection (≤ 4 samples), for dose titration at week 18, 24, and scheduled visits thereafter, and these samples will be analysed only if the participants took at least 1 dose of study drug using LC/MS-MS method in bioanalytical facility, and results will be reported for information purpose.

Blood loss:

For each participant, the total volume of blood withdrawn is approximately 614 mL for 45 participants / 418

mL for rest of the participants over a period of 52 weeks as detailed below:

Sample Type	Sample Volume up to (mL)	Number of Sampling Times		Volume (mL)		Comments
		For 45 subjects	For rest of the subjects	For 45 subjects	For rest of the subjects	
Initial Screening	15	1	1	15	15	1 visit
Qualifying TT levels	5	4	4	20	20	visit 1a, visit 1b & visit 1c and additional if needed
Treatment and Extension phase laboratory assessments and / or TT C_{trough} samples for dose titration	15	5	5	75	75	week 1, week 12, week 24, and scheduled visits thereafter i.e., week 36, week 42
Albumin, SHBG, and TT C_{trough} samples for dose titration	10	4	4	40	40	week 6, week 18, and scheduled visits thereafter i.e., week 30, week 42
For PK	10	39	20	390	200	As per PK sample table
For Potential Extra Blood loss	N/A	N/A	N/A	20	20	N/A
Saline Blood Loss (if applicable)	0.5	17	5	9	3	(if applicable)
Serum TT and informative purpose (analysis at Bioanalytical facility for participants who have taken at least 1 dose of study drug)	5	9	9	45	45	screening, visit 1a, visit 1b & visit 1c and additional visit if needed in screening, week 18, 24 visits, and scheduled visits thereafter i.e., week 30, week 36, week 42
			Total	**614**	**418**	

6.4 Meals

Participants will be provided with standard meal at appropriate intervals before and after study drug administration during the housing period as per local norms.

6.5 Blood Sample Processing

The blood sample collection, processing and storage for both clinical laboratory and bioanalysis will be included in the manual / plans with complete instructions provided prior to collection of study specific blood sample. This manual / plan will be included in the trial master file.

6.6 Bioanalytical Procedure and Sample Analysis

6.6.1 Sample Analysis

Samples will be assayed for determination of TT, DHT, DHTC, E2 and Testosterone Cypionate using a validated LC-MS/MS method at the Bioanalytical facility as per In-house SOPs, USFDA guidelines and GLP practices.

All samples from each participant will be analyzed on the same standard curve. Quality control samples will be distributed throughout each batch of study samples assayed as per In-house SOPs. Samples with drug concentrations greater than the upper limit of validation range of the assay will be diluted with the appropriate drug-free biological fluid and re-assayed. Concentrations, which are below the lower limit of quantitation (LLOQ) will be reported as BLQ and will be considered as zero for PK calculations.

All of the collected samples will be analyzed. Samples collected from withdrawn/dropped participants from the study will also be assayed and presented except in the following cases:

If any participant is dropped or withdrawn after dosing, and no post-dose samples are collected, then the pre-dose sample of such participant will not be analyzed.

Note:

The additional (maximum of 9) samples collected for serum TT at selection (≤ 4 samples), and for dose titration at week 18, 24, and scheduled visits thereafter will only be analysed for cross-validation only if the participants took at least 1 dose of study drug using LC/MS-MS method in bioanalytical facility, and results will be reported for information purpose.

Bioanalysis may be initiated after completion of Week 12 full PK profile of all the participants.

6.6.2 Procedure for Reanalysis

Repeat analysis will be performed and reported as per In-house SOPs. Incurred sample reanalysis (ISR) will be performed as per In-house SOPs.

6.6.3 Recording and Reporting of Drug Concentrations

Concentrations of analytes will be presented as per In-house SOPs.

6.7 Pharmacokinetics Analysis

If a Pharmacokinetics Analysis Plan (PKAP) is written for this study, it will supersede any information listed

in the protocol.

6.7.1 Data Entry

Participant-wise generated concentration-time data of serum testosterone levels will be transferred electronically from the Bioanalytical facility to the Pharmacokinetics & Biostatistics facility.

6.7.2 Pharmacokinetics Analysis

PK parameters for serum testosterone will be calculated using Phoenix WinNonlin software Version 8.5 (or higher) by non-compartmental analysis.

Actual time of collection of blood samples will be used in pharmacokinetic analysis. PK parameters for serum total testosterone will be calculated as follows:

Primary PK Parameters	
$C_{avg\ 168h}$	Average serum concentration at 168 hour
Secondary PK Parameters	
$AUC_{0\text{-}168h}$	The area under the serum concentration versus time curve, from time 0 to 168 hour post-dose, as calculated by the linear trapezoidal method.
$AUC_{0\text{-}\infty}$	The area under the serum concentration versus time curve from time 0 to time infinity. $AUC_{0\text{-}\infty}$ is calculated as the sum of the $AUC_{0\text{-}t}$ plus the ratio of the last measurable plasma concentration (Ct) to the elimination rate constant λ_z.
C_{avg}	Average serum concentration at steady state
C_{min}	Minimum serum concentrations at steady state
C_{max}	Maximum measured serum concentration over the time span specified
T_{max}	Observed time of maximum serum concentration

6.7.3 Pharmacokinetics Datasets

Full **PK population:** The PK population consists of all participants in the study who have completed 12 weeks of study treatment with calculable AUC, C_{max} and C_{avg} from 168 -hour PK assessment at Week 12 with no significant protocol deviation.

PK population: The PK population consists of all participants who receive study treatment and have at least one evaluable 168-hour PK profile of study treatment with calculable AUC, C_{max} and C_{avg} from 168 -hour PK assessment at any scheduled full PK assessment visit (Week 1, Week 6, or Week 12).

Note: The data from time points that exhibit values which are below the lower limit of quantification and reported as 'BLQ' will be considered as "0" for all PK evaluations.

The following participants who completed at least 1 week of the study and who's serum samples are analyzed for drug concentration may not be included in the PK analysis if:

- Participants who have insufficient data points to allow for meaningful estimation of the PK parameters C_{max} or AUC. However, if the participant has adequate sampling time points to sufficiently characterize the absorption phase of drug substance, such participant may be considered for PK analysis of C_{max} parameter only.
- No values of $AUC_{0\text{-}inf}$ will be reported for cases that do not exhibit a log-linear relationship in the terminal elimination phase in the concentration versus time profile.
- At week 1, 6 and week 12 sampling, if a participant misses at least 3 consecutive time points, the data from this participant will be excluded for the determination of C_{avg}, $AUC_{0\text{-}168}$ and AUC_{inf}.
- Subject misses scheduled dosing at week 12.
- Primary efficacy end point will be analysed with Full PK population data.

7. Assessments of Safety

Safety assessments in this study include evaluation of all AEs noted during study participation, drug or device-related adverse events, changes in concomitant medication during study participation (including change in dose), vital signs (Pulse rate, axillary body temperature, respiratory rate, Blood pressure), ECG, physical examinations, laboratory examinations (except serology) and ABPM from baseline through the duration of the study.

7.1 Safety Monitoring

Safety monitoring will be carried out by a licensed/qualified physician or nurse practitioner at the time of check-in, throughout the study at scheduled time points, and as needed at the Investigator's discretion.

7.1.1 Vitals and Participant Well-being:

a. Vitals (axillary body temperature, pulse rate, Respiratory Rate and blood pressure) will be examined at initial screening, TT Qualification (Visit 1a, 1b and 1c), and during study period as stated in section 17.1 Appendix: Table of Study Assessment and Schedule of Events
b. Vitals (Body temperature, Pulse Rate, Respiratory Rate and Blood Pressure) will also be examined during occurrence of an AE/s or termination/withdrawal of participant from the study and as per the clinical condition of the participant as judged by the physician, other than above scheduled times.
c. Blood Pressure (SBP/DBP) will be measured in sitting position. If measured in supine position the same will be documented in Case Report Form.
d. Participant's well-being will be verified at the time of vitals examination.

Additional safety evaluations (including, but not limited to Vitals, ECG, Laboratory investigations) shall be performed as per investigator discretion to ensure safety and well-being of the participants.

7.1.2 Ambulatory Blood Pressure Monitoring (ABPM)

ABPM will be evaluated in each participant continuously for a period of 24 hours (from 0.5 hours pre-dose to 24 hours post-dose) at the following time-points: Baseline/pre-dose (week -1 to day 1*), day 1 of week 12, day 1 of week 24, and scheduled visits thereafter.

If the subject misses ABPM evaluation on the scheduled day, the subject will be encouraged to perform on the next day to complete the 24-hr ABPM evaluation.

*: could be during domicile or ambulatory, but it should be completed before day 1/week 1 dose administration.

7.1.3 Participant well-being questionnaire

In order to evaluate potential dependence and withdrawal after abrupt discontinuation of therapeutic doses of testosterone, depression, suicidality, and insomnia and other symptoms will be assessed based on the following as outlined in 17.1 “Table of Study Assessment and Schedule of Events”.

a. Columbia-Suicide Severity Rating Scale (C-SSRS) for Suicidality assessment
b. I-PSS
c. Aging Males’ Symptoms (AMS)
d. Patient Global Impression of Change (PGI-C)
e. Hamilton Depression Rating Scale (HDRS)
f. SF-36
g. Self-Injection Assessment Questionnaire (SIAQ),
h. Assessment of Essential Tasks Questionnaire

7.2 Adverse Events

All observed or volunteered adverse events (AEs), and their suspected causal relationship to the study drug will be recorded in the participant’s medical records and on the adverse event page(s) of the eCRF.

AEs will be documented between the start of the study (after the signature of ICF) to safety follow-up or early termination visit (ET), whatever is first.

Treatment-emergent Adverse Events (TEAEs), including intensity, seriousness, and relatedness to study treatment as well as action taken, will be recorded between the start of study treatment to safety follow-up

visit. All AEs will be coded according to MedDRA (the latest version available) by system organ class (SOC) and preferred term.

Untoward effects detected in the time interval between the inclusion of the participant and the start of study treatment will be recorded as medical history, and not be included in the analysis of TEAEs. Events involving adverse drug reactions, illnesses with onset during the study, or exacerbation of pre-existing illnesses will be recorded. For all AEs, the onset, duration of symptoms and signs, treatment and relationship to the study drug will be noted on the adverse event page of the eCRF.

7.2.1 Definitions of Adverse Events

The following International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) AE definitions apply to this study:

Adverse Event (AE): Any unfavourable medical occurrence in a trial participant administered the investigational product. The adverse event does not necessarily have a causal relationship with the treatment.

Serious Adverse Event (SAE): Any unfavourable medical occurrence that is considered serious at any dose if it:

- Results in death.
- Is life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital abnormality/birth defect.
- An important medical event that may not be immediately life-threatening or result in death or hospitalisation, that may jeopardise the participant or that may require intervention to prevent serious outcomes (see ICH E2A and E19) should generally be considered as serious.

An adverse drug reaction (ADR) is defined as a response to a drug that is noxious and unintended and that occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of diseases or for modification of physiological function.

Suspected Unexpected Serious Adverse Reaction (SUSAR): an adverse reaction that meets three criteria: suspected, unexpected and serious.

• Suspected: There is a reasonable possibility that the drug caused the adverse drug reaction

Unexpected: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure or alternative documents according to applicable regulatory requirements; see RSI).

• Serious: Refer SAE

7.2.2 Assessment and Documentation of the Adverse Events

Adverse events will be assessed beginning at enrollment (date of signed informed consent) and up to the end of the follow-up visit.

At each visit, participants will be asked a standard nonleading question (such as "How have you felt since your last visit") to elicit any medically related changes in their well-being. They will also be asked if they have visited an emergency room/urgent care clinic or have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (see Section 7.2.8).

In addition to participant observations, AEs identified from any study data (e.g. vital sign data, physical examination findings) or identified from the review of other documents (e.g. participant diaries) that are relevant to participant safety will be documented on the AE page in the eCRF.

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study medication or their clinical significance.

Severity

The severity of unsolicited AEs will be characterized as "mild", "moderate", or "severe" according to the following definitions:

Mild	Moderate	Severe
Events are usually transient and do not interfere with the participant's daily activities.	Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities.	Events interrupt the participant's usual daily activity.

Relationship

The causal relationship between the study drug and the AE has to be characterized as related, unrelated, unlikely, possible, probable, or unknown (unable to judge).

Causality Assessment

Related	Events can be classified as "related" when there is a direct possibility that the study drug causes AE.
Unrelated	Events can be classified as "unrelated" if there is not a reasonable possibility that the study drug caused the AE.
Unlikely	An "unlikely" relationship suggests that only a remote connection exists between the study drug and the reported AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant medication, appear to explain the reported AE.
Possible	A "possible" relationship suggests that the association of the AE with the study drug is unknown; however, the AE is not reasonably supported by other conditions.
Probable	A "probable" relationship suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator's clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression or expression of disease state or concomitant medication reactions) do not appear to explain the AE.
Unknown	All efforts should be made to classify the AE according to the above categories. The category "unknown" (unable to judge) may be used only if the causality is not assessable, e.g., because of insufficient evidence, conflicting evidence, conflicting data, or poor documentation.

7.2.3 Abnormal Lab Results

The criteria to determine whether an abnormal test result should be reported as an AE are as follows:

- When the test result is accompanied by an associated symptom.
- When the test result leads to a change in the study drug dose or study discontinuation.
- When the test result leads to an introduction of a significant concomitant drug treatment or other therapy.
- When the test result leads to any of the outcomes included in the definition of SAE.
- When the test result is considered by the Investigator as an AE result requiring an additional diagnostic examination or medical/surgical intervention.

7.2.4 Safety Monitoring Plan

As part of safety monitoring plan, the below rules should be followed. The trial should be halted based on below criteria:

a) Death in any participant in which the cause of death is judged to be probably or definitely related to the study drug by the treating investigator.
b) The occurrence in any participant of a life-threatening SAE that is assessed to be related to the study drug by the treating investigator.
c) Two occurrences of Grade 3 or higher toxicities that are assessed to be related to the study drug by the treating investigator.
d) Two occurrences of a clinically significant Grade 3 or higher laboratory abnormality assessed to be related to the study drug by the treating investigator.

7.2.5 Toxicity Grading Scale

AEs will be evaluated and treated by the Principal Investigator or designee. The intensity or severity of AEs will be graded as per below Toxicity Grading Scale Tables.

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participant should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/ vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock

Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with Activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Illness or clinical AE	No interference with Activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

B. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150

Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** "ULN" is the upper limit of the normal range.

Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 – 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate

7.2.6 Reporting Adverse Events

Adverse Events

All AEs that occur in a participant from the time the participant signs the ICF for the study, regardless of severity, causality, and whether or not they occurred during the course of the trial are to be recorded in the appropriate AE pages (either 'serious' or 'non-serious') in the eCRFs. The investigator shall complete all the details requested including dates of onset, severity, action taken,

treatment measures, outcome, and relationship to the study drug, and any other treatment measures undertaken. Each event should be recorded separately.

At the End of the study visit, participants will be queried regarding any AEs that have occurred since the Treatment visit. Participants will be asked to volunteer information with a non-leading question such as, “How have you felt since your last visit?” Study center/site personnel will then record all pertinent information in the participant’s eCRF.

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes the date of onset, description of AE, investigator-specified severity, relationship to study medication, action taken, outcome and date of resolution. AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed up to adequate resolution. Adverse events and abnormal laboratory parameters will be followed up till the values return to baseline, acceptable levels, show a tendency towards resolution, or until 30 days from the last dose, or until the Investigator is of the opinion that follow-up is no longer required. The latest version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the participant is screened but does not deteriorate will not be reported as an AE. However, if it deteriorates at any time during the study, it will be recorded as an AE.

Any AE that meets SAE criteria (Section 7.2.1) must be immediately (i.e. within 24 hours after the time study site personnel awareness about the event) reported on the SAE page in the eCRF.

Serious Adverse Events

Within 24 hours of awareness of any AE that meets one of the criteria for an SAE, the Investigator must report the event to the sponsor/CRO, Licensing authority and independent ethics committee (IEC) as per applicable regulatory requirements. Sponsor/CRO and Investigator shall send the SAE report after due analysis to the Licensing authority, ethics committee and head of the institute where the trial is being conducted within 14 days of knowledge of the occurrence. The investigator shall ensure that the ethics committee shall send the SAE report and its opinion on financial compensation within 30 days to the licensing authority. The sponsor shall pay compensation as per the orders by the licensing authority within 30 days of receipt of orders from the licensing authority. A follow-up report shall be sent to the sponsor/CRO, Licensing authority, and head of the institute where the trial is conducted within 14 days of the occurrence of SAE which shall include the outcome and treatment provided. If, during follow-up, any non-serious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

If the SUSAR is fatal or life-threatening, associated with the use of the study drug, and unexpected, Regulatory Authorities and IECs will be notified within 7 calendar days after event onset. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported within an additional 8 days (15 days total).

If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with the use of the study drug, and unexpected, Regulatory Authorities and IECs will be notified within 15 calendar days of event onset.

The Sponsor will notify the Investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of participants. Follow-up information may be submitted if necessary.

The Sponsor will also provide annual safety updates to the Regulatory Authorities and IECs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

The study center must transmit the SAE form to the SAE email to the CRO. SAE form (as per NDCT 2019, Table 5) or study specific SAE form shall be sent to the licensing authority and IEC which accorded approval at the site. Even if an initial report is made aware by the site personnel telephonically to the sponsor or CRO representative, an SAE form completed with all available details must still be faxed within 24 hours of knowledge of the event at the study center/site. Supplemental information shall be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, treatments administered for the events, holding and observation notes, discharge summaries, autopsy reports, and death certificates. The Investigator is expected to take all therapeutic measures necessary for the resolution of the SAE. Any medications or procedures necessary for the treatment of the SAE must be recorded on the appropriate pages of the participant's eCRF and SAE form. All SAEs are to be followed up by the study staff until resolution or until the SAE is deemed stable. The Sponsor or CRO may contact the study center to solicit additional information or follow up on the event. The original eCRF pages should be returned immediately to the eCRF binder.

The information must include at least the following:

- Name, address, and telephone number of the reporting Investigator.
- Study drug and Protocol Number.
- Participant identification number, initials, sex, and date of birth.
- Description of the SAE, measures taken, and outcome.
- Preliminary classification of causal relationship by the Investigator. Additional follow-up information should be completed on an SAE follow-up form with a copy sent to the Sponsor /CRO and the original placed in the SAE section of the eCRF binder.

In the case of fatal or life-threatening events please also immediately telephone the Safety Surveillance and Reporting Unit.

The investigator or designee must e-mail the documentation to the drug safety mailbox (drugsafety@amneal.com) shown in the table below.

Serious Adverse Event ReportingEmergency Contact Details:

Drug Safety Contact E-mail:
Sponsor's Medical and Safety Expert Name : Ronald Sanwo, M.D, MPH Representative, Pharmacovigilance Safety Physician to, Amneal Ireland Limited Tel. No. +1-877-835-5472 Fax: 631-983-2591 Email: drugsafety@amneal.com

7.2.7 Follow-Up of Participants Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF.

For SAEs, follow-up information to an initial safety report must be provided by the investigator as soon as the relevant information is available. Relevant information such as discharge summaries, autopsy reports, and medical consultations will be reviewed in detail by the investigator and discussed with the medical monitor as appropriate.

All SAEs or AEs that lead to discontinuation of study medication will be followed up until satisfactory resolution, the investigator deems the event to be chronic or not clinically significant, or the participant is considered to be stable.

7.2.8 Concomitant Medications

Any medication taken during the study other than the IMP/study-issued treatment is defined as a concomitant medication and will be documented in the eCRF.

All participants must be able to stop their current hypogonadal medications for the study duration. The Principal Investigator/Clinical Investigator/Attending Physician will decide whether to continue the participant in the study if the participant requires concomitant medications during the study. The decision will be based on the following:

- If there is a likelihood of PK interactions with the investigational product and/or with other medications given during the course of the study.
- Depending on the time and duration of concomitant medications

For previous and current concomitant medications, the following information (along with any change in medication) will be recorded in eCRF:

- Name of medication
- Dose (total, unit)

- Regimen (e.g., once daily, twice daily, three times daily)
- Start date, end date, ongoing
- Indication
- Route
- Whether or not it was associated with an AE

It is the responsibility of the investigator to ensure that details regarding the medication, and as necessary withdrawal are recorded in full in the eCRF.

7.2.9 Demographics, Physical Examination and Vital Signs

A complete physical examination or symptom based physical examination assessment, DRE (whenever performed) and vital signs (including blood pressure, axillary body temperature, respiratory rate and pulse rate) will be performed as per 17.1 "Table of Study Assessment and Schedule of Events; height only needs to be collected at the screening visit.

All data collected from the physical examinations, DRE and vital sign assessments must be available in the source documents and will be added to the analysis database. An abnormal vital sign value or physical examination finding at the screening visit will be captured in the medical history. An abnormal vital sign value or physical examination finding at the end of the treatment visit that has worsened since the screening visit will be captured as an AE.

7.2.10 Electrocardiogram

A standard 12-lead electrocardiogram (ECG) assessment will be performed locally at the study site during the screening visit, at week 1, week 12, week 24, and scheduled visits thereafter and following standard procedures at the study site. Data collected from the ECG assessments must be available in the source documents and will be added to the analysis database. Any abnormal ECG value noted at the screening visit will be captured in the medical history.

7.2.11 Blood glucose monitoring and Management of anti-diabetic Medication in patients with Diabetes

Participants with diabetes mellitus must meet the protocol-specified inclusion criterion of HbA1c ≤ 9.0% or as per PI's discretion at screening.

Type 2 Diabetes Mellitus (T2DM): Participants with T2DM who meet the glycated hemoglobin (HbA1c) with stable doses of medication inclusion criterion may be enrolled.

Type 1 Diabetes Mellitus (T1DM) or insulin-treated diabetes: Participants with T1DM or insulin-treated diabetes who meet the HbA1c inclusion with stable doses of medication criterion may be enrolled; however, due to the potential for changes in insulin sensitivity associated with testosterone treatment, closer monitoring is recommended.

Hence, blood glucose levels for diabetic patients will be monitored (self) throughout the study period once in a week, and fasting glucose and HbA1c periodically throughout the duration of the study and documented in the participant's diary for glucose (refer stated in section 17.1 "Table of Study Assessment and Schedule of Events).

For both T2DM and T1DM participants, any patient-specific adjustments to insulin or other antidiabetic medications can be made based on the blood glucose levels at the discretion of the treating physician / qualified health care professional and documented in accordance with Standard of Care. The changes if any in the standard of care medication for diabetes will be documented at the appropriate study visit specific medical records of participant with diabetes.

7.3 Laboratory Analysis

Laboratory testing will be performed at a central/clinical laboratory as per 17.1 "Table of Study Assessment and Schedule of Events". Pre-defined Laboratory assessments will be obtained, with the laboratory assessments in Table 7.4 collected at a minimum. Additional blood draws may be needed if clinically indicated, as determined by the investigator.

Any data collected from the laboratory testing must be available in the source documents and will be added to the listings. An abnormal laboratory value at the screening visit will be captured in the medical history.

Table 7.4: Laboratory Assessments

Hematology	Biochemistry	Urinalysis	Serology
Hemoglobin, Hematocrit, RBC count Platelet count, WBC count Total neutrophils (absolute), Eosinophils (absolute), Monocytes (absolute), Basophils (absolute), Lymphocytes (absolute)	Fasting Blood glucose, Urea, Creatinine,Sodium, Potassium, Alanine aminotransferase, Aspartate aminotransferase, Total bilirubin, Alkaline phosphatase, Uric acid, Total protein, Lipid profile [TC, TG, HDL-C, LDL-C, VLDL-C]	microscopic examination pH, Glucose (qualitative), Protein (qualitative)Blood (qualitative), Ketones, Nitrites, Leukocyte esterase,	HIV Hep B Hep C
PSA: **Endocrine function** [Total and Free Testosterone, Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), Growth Hormone, Estradiol, Prolactin, Cortisol, and Thyroid function tests (TSH, T3, T4)]; **HbA1c**: Glycated hemoglobin. **Coagulation tests: Prothrombin Time (PT), activated Partial Prothrombin Time (aPTT)** **International Normalized Ratio (INR)** Albumin and Sex hormone Binding Globulin (SHBG) **Urine Drug Screen:** Amphetamine, Barbiturates, Benzodiazepines, Cocaine, Marijuana-THC, MDMA (3, 4-methylenedioxymethamphetamine [Ecstasy]), Methadone, Methamphetamines, Opioids, Opiates and Phencyclidine			

8. Statistical Considerations

Before database lock and unblinding, a separate statistical analysis plan (SAP) will be finalized, providing detailed methods for the analyses as outlined in the following subsections. Any deviations from the planned analyses will be described and justified in the final clinical study report. The study is powered for the primary efficacy endpoint assessed at Week 12, with safety evaluated through Week 24 as part of the primary evaluation period.

8.1 Study Disposition

The Participants will be listed and summarized by treatment/dose and participant ID. Statistical analyses will be performed on all the participants who have taken the study dose at least once. Safety Analysis will be performed on all the participants who have provided the informed consent and who took at least 1 dose of study drug. Participants withdrawn before dosing of first dose will not be used for statistical analysis.

Number and percentage of participants taken one dose of study medication, number and percentage of participants completing the study, number and percentage of participants who were withdrawn in the study along with the reasons of withdrawal and number of percentages of participants in each analysis sets will be tabulated.

In addition, the number of patients enrolled, administered and completed will be tabulated by treatment group.

Additionally, all the minor and major protocol deviations will be defined in the final SAP.

8.2 Analysis Datasets

Statistical dataset will be the same as the PK dataset. Participants who completed the study will be considered for statistical analysis.

Statistical analysis will be performed on the basis of efficacy and safety of the treatment received.

Statistical analysis will be performed on the following populations:

Full Analysis Set (FAS): This population consists of all participants who have received at least one dose of the study drug.

PK population: The PK population consists of all participants who receive study treatment and have at least one evaluable 168-hour PK profile of study treatment with calculable AUC, C_{max} and C_{avg} from 168 -hour PK assessment at any scheduled full PK assessment visit (Week 1, Week 6, or Week 12).

Full PK population: The PK population consists of all participants in the study who have completed 12 weeks of study treatment with calculable AUC, C_{max} and C_{avg} from 168 -hour PK assessment at Week 12 with no significant protocol deviation.

Safety population: The safety population consists of all participants who took at least 1 dose of study drug.

8.3 Data Analysis

8.3.1 Primary Efficacy Analysis:

The primary efficacy endpoint in the study will be percentage of participants with average serum Total Testosterone concentration ($C_{avg\ 0\text{-}168h}$) over the 7-day dosing interval (0-168 hours) within the defined range of 300 to 1100 ng/dL at week 12 using full PK population data.

The primary endpoint will be analyzed via analysis of covariance (ANCOVA) models with two-sided, 95% confidence interval. The primary endpoint will be satisfied if ≥75% of participants have serum Total Testosterone Ca_{vg168h} within the range of 300 to 1100 ng/dL at Week 12, with a lower bound of the 95% confidence interval (CI) at ≥65%.

The primary efficacy endpoint, $C_{avg\ 168h}$, is calculated from the AUC using the following formula:

$$C_{avg\ 168h} = AUC\ (0\text{-}168\ h) / 168$$

8.3.2 Key Safety Endpoints:

i. Percentage of participants with maximum (peak) serum Total Testosterone concentration (C_{max}) <1500 ng/dL. This endpoint will be satisfied if ≥85% of participants have serum Total Testosterone C_{max} <1500 ng/dL at Week 12 of treatment.

ii. Percentage of participants with serum Total Testosterone C_{max} between 1800 to 2500 ng/dL, (inclusive). This endpoint will be satisfied if <5% of participants have Total Testosterone C_{max} in this range of 1800 to 2500 ng/dL, inclusive at Week 12 of treatment.

iii. Number of participants with serum Total Testosterone C_{max} >2500 ng/dL. This endpoint will be satisfied if no participants have serum Total Testosterone C_{max} >2500 ng/dL at Week 12 of treatment.

8.3.3 Additional Secondary Efficacy Analysis

i. Number and percentage of participants with minimum serum Total Testosterone concentration (Cmin) <300 ng/dL at Week 12 of treatment

ii. Serum Total Testosterone Cavg168h within the defined range of 300 to 1100 ng/dL for the 75 mg dose of the auto-injector (that is, excluding participants on the 50 mg and 100 mg

dose) at Week 12. Endpoint will be satisfied if ≥75% of participants with a lower limit of the 95% CI at ≥65%, have serum Total Testosterone Cavg168h within the defined range of 300 to 1100 ng/dL at Week 12 of treatment.

iii. Assuming sufficient numbers of participants received the 100 mg dose of the auto-injector, the serum Total Testosterone Cavg168h at Week 12 will be calculated and presented with descriptive statistics.

iv. Assuming sufficient numbers of participants received the 50 mg dose of the auto-injector, the serum Total Testosterone Cavg168h at Week 12 will be calculated and presented with descriptive statistics.

v. Single-dose area under the curve (AUC), C_{max}, time to maximum serum concentration (T_{max}), and Cavg168h of Total Testosterone for the 75 mg dose of auto-injector in a sub-set of participants (with PK Population data).

8.4 Interim and DSMB Anlayses

There will be no interim analysis performed during the study.

8.5 Missing Data

Details on the handling of missing data will be provided in the SAP.

8.6 Demographic and Baseline Characteristics

All demographic analysis (like date of birth, age, gender (male), height, weight, BMI, race, ethnicity, etc.,) will be summarized by treatment group for all the enrolled participants and listing will be provided by participant number and treatment group. Medical history, smoking history and other baseline characteristics will be summarized using number and percentage and will be listed by participant number and treatment group.

8.7 Prior Medication and Concomitant Medication

Prior Medication and Concomitant Medication will be coded using World Health Organization Drug Dictionary (WHO-DD). Prior medication are those medications that are taken before the administration of study treatment to the participant. Concomitant Medication are those medications that are taken from the time of administration of first dose of study treatment to the participant until end of the study. Any medication that are started prior the study treatment but are continued after dosing will be considered as concomitant medication.

8.8 Treatment Compliance

Compliance to the medication will be calculated and for the treatment period. The compliance will be defined as

$$\text{Study Drug Compliance} = \frac{\text{No. of doses taken by the participants}}{\text{Total Number of doses prescribed}} \times 100$$

The compliance will be summarized and listed for all the participants by treatment dose group.

The accepted Full PK population used for pivotal efficacy evaluation includes each participant who meets all the inclusion/exclusion criteria, administers a prespecified proportion of the scheduled doses (e.g., not less than 85% primarily in the treatment phase- first 12 weeks) of the assigned product for the specified study duration, does not miss the scheduled dosing for more than 1 dose during the 12-week period, and completes the study with no protocol violations that would affect the treatment evaluation or primary outcome of the study.

The accepted population for safety evaluation includes each participant who meets all the inclusion/exclusion criteria, administers a prespecified proportion of the scheduled doses (e.g., not less than 85% primarily in the treatment phase and continued safety follow-up) of the assigned product for the specified study duration, does not miss the scheduled dosing for more than 2 doses during the first 24-week period, and completes the study with no protocol violations that would affect the treatment evaluation or primary outcome of the study.

8.9 Confidence Interval (CI)

95% CI will be determined for the participants who have serum Total Testosterone $C_{avg\ 168h}$ concentrations within the range of 300-1100 ng/dL at Week 12.

8.9.1 Safety Endpoints

The safety endpoints are as follows:

- ECG, Vitals (Pulse rate, Axillary Body Temperature, Respiratory rate, Blood pressure)
- Adverse events
  - Treatment-emergent adverse events (TEAEs)
  - Drug-related AEs
  - SAEs
  - Device related AEs

- Physical examination
- Laboratory examination assessments (except serology) from baseline to week-52.
- Use of anti-hypertensive medications (new initiation or dose adjustment)
- Change from baseline in 24-hour mean systolic and diastolic blood pressure measured by continuous Ambulatory Blood Pressure Monitoring (ABPM) at Week 12, week 24, and scheduled visits thereafter.

The safety data will be based on the safety population dataset. Further details of the safety analyses will be provided in SAP.

Safety will be assessed throughout the study up to the post treatment safety follow up visit. The participant's well-being will be checked up to 7 -14 days after end of treatment unless any AE/SAE warrants a further follow-up.

Statistical Analysis of Data Through Week 24

The primary objective of this pivotal Phase 3 study is to evaluate the efficacy and safety of the testosterone cypionate auto-injector administered subcutaneously once weekly for 12 weeks in adult males with hypogonadism. The primary efficacy endpoint is assessed during the initial 12-week treatment period. The study is powered for the primary efficacy endpoint assessed at Week 12, with safety evaluated through Week 24 as part of the primary evaluation period.

Safety data collected through Week 24 is considered sufficient to characterize the safety profile of the investigational product and to identify potential safety signals following continued exposure beyond the primary efficacy assessment period. Accordingly, the statistical analysis will include evaluation of the primary efficacy endpoint assessed through Week 12 and cumulative safety data collected through Week 24.

The study employs a single active treatment with blinded dose strengths. To facilitate the planned statistical analysis of data through Week 24, an independent statistician who is not otherwise involved in the conduct of the study will be unblinded to treatment assignment solely for the purpose of conducting the statistical analysis. Study participants and the clinical staff responsible for conducting study assessments will remain blinded to the assigned dosage strength in accordance with the protocol, and unblinding of the independent statistician will not affect ongoing study conduct, procedures, or the integrity of the blinded study design.

A clinical study report will be prepared based on the analysis of efficacy data through Week 12

and safety data through Week 24 and submitted to the Agency.

Subjects may continue participation beyond the 24-week primary evaluation period, with additional safety data collected at scheduled visits. Available safety data collected after Week 24 will be provided to the Agency as appropriate.

.

Detailed methodology and specifications for all analyses will be described in the Statistical Analysis Plan (SAP).

8.10 Sample Size Calculations

To estimate sample size for the phase 3 trial, Amneal developed and validated a Population PK model to simulate steady state concentrations of the Test Product at week 12. Assuming a minimum success rate of 90% for the primary endpoint based on $C_{avg0\text{-}168}$ (Week 12 C_{avg} total testosterone concentration within the prespecified normal range of 300-1100 ng/dL), the study would need to finish with 60 subjects/participants to obtain a lower bound of the 2-sided 95% CI that would be equal to or exceed 65%. Assuming a dropout rate of 25%, a minimum of 80 subjects (for example 80-140 subjects) will need to be enrolled to ensure that at least 60-120 subjects complete the study.

Simulations to Estimate Sample Size With 75 mg As the Starting Dose				
Sample Size (n)	**Mean Passing Rate ($C_{avg0\text{-}168}$) (%)**	**95% LCI ($C_{avg0\text{-}168}$) (Mean)**	**Week 12: Studies Meeting Criteria (%)**	
			Based on $C_{avg0\text{-}168}$* (%)	**C_{max} > 2500 ng/dL (%)**
Passing scores	≥ 75.0	≥ 65.0	> 80	> 80
14 obs in silico	*92.9*	*66.1*	*N/A*	*N/A*
14	85.7	58.0	36.0	100
20	99.0	81.6	100	99.3
40	98.9	89.3	100	99.3
60	98.9	92.2	100	98.7
80	98.9	93.6	100	98.3
100	98.9	94.4	100	98.3
120	98.9	95.1	100	98.0
140	98.9	95.5	100	97.3

160	98.9	95.8	100	97.0

***Note:** Results based on 300 simulated clinical trials for all sample sizes, except for n=14 which was based on one *in silico* trial for the observed and 100 simulated clinical trials.
N/A: Not Applicable

8.11 Description of Subgroups to be Analyzed

Subgroup analyses for the primary and key secondary endpoints will be performed by age group, race/ethnicity, BMI, and other baseline characteristics of interest.

Statistical Analysis Methodology and General Consideration

Statistical analysis will be performed using SAS software Version 9.4 or higher.

Summary statistics of the data collected will be provided by treatment group. Continuous variables will be summarized using the mean, SD, CV, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Participant data listing will be provided for the important variables captured in the study. All statistical tests will be 2-sided and will be performed at the 5% level of significance, unless otherwise specified. Details of the statistical analyses, methods, and data conventions will be further described in the Statistical Analysis Plan (SAP).

8.11.1 Safety Analyses

8.11.1.1 Adverse Events

All adverse events (AEs) will be reported, whether or not they are considered to be related to the treatment. The report of each AE should include the date of onset, description of AE, severity, relation to study medication, action taken, outcome, and date of resolution.

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) current version or higher summarized by treatment group. Summary tables of AEs comparing the type, incidence, severity and relationship will be prepared by treatment group.

All participants who are qualified for the treatment of the study will be included in the comparative safety analysis.

8.11.1.2 Other Safety Parameters

Other Parameters for safety analysis are as follows:

- Vitals (Pulse rate, Axillary Body Temperature, Respiratory rate, Blood pressure) at minimum will be tabulated using n, mean, SD, median and Range (min, max)
- Physical examination will be summarized using number and percentages.

- ECG parameters including heart rate, PR interval, QRS duration, QT interval, and corrected QT interval (QTc) will be evaluated. Safety endpoints will include change from baseline in ECG parameters and the incidence of clinically significant ECG abnormalities, including QTc prolongation. Descriptive statistics at a minimum, Mean, Median, and Range (min, max), Change from baseline.
- ABPM: Change from baseline in 24-hour mean systolic and diastolic blood pressure measured by continuous ABPM at Week 12, week 24, and scheduled visits thereafter.
- Use of anti-hypertensive medications (e.g. new initiation or dose adjustment)
- Change from baseline in quality of life based on C-SSRS, HDRS, SIAQ, SF-36, Assessment of Essential Tasks Questionnaire at Week 24, and scheduled visits thereafter.
- Concomitant medications will be classified according to the World Health Organization (WHO) Drug Dictionary and will be tabulated by treatment and presented as data listings.
- Laboratory safety assessment (i.e., biochemistry, hematology and urinalysis) will be assessed by Investigators for the presence of any findings that meet the description of an AE. However, Laboratory test results will be tabulated using n, mean, SD, median and Range (min, max) for all the continuous variables and using number and percentages for all the categorical variables.

The safety data will be based on the safety population dataset. Further details of the safety analyses will be provided in SAP.

8.12 Deviations from the Planned Statistical Analysis

Any changes to the planned analysis (as described in the protocol and SAP) post database lock will be amended and will be documented in the clinical study report (CSR).

This section describes the bio-statistical analysis as foreseen at the time of planning the study. Changes, additions and further details about the analyses will be described in the SAP. After the finalization of the SAP, any additional analyses or changes to analyses that may be required will be fully disclosed in the CSR.

8.13 Data Quality Assurance

Data will be entered into an electronic data capture system. Management of clinical data will be performed in accordance with applicable Amneal or its designee's standards and data cleaning procedures to ensure the integrity of the data (e.g., removing errors and inconsistencies in the data). A clinical study report will be prepared based on efficacy data through Week 12 and safety data through Week 24 and submitted to the Agency. Additional safety data collected beyond Week 24 will be provided as available.

This Clinical Study Report (CSR) will be prepared in accordance with the guidelines provided by the International Conference on Harmonisation (ICH) E3 Guideline for Structure and Content of Clinical Study Reports. The CSR will summarize the key aspects of the clinical trial, including study design, methods, results, and conclusions. The report will follow a standardized structure to ensure transparency, accuracy, and compliance with regulatory requirements.

The Clinical Study Report will undergo data quality checks including Data verification for accuracy along with consistency checks to ensure that data matches across sections. Statistical validation is essential to confirm the accuracy of analyses. Regulatory compliance with guidelines like ICH E3 is required for successful submission. Adherence to protocols and cross-functional reviews ensures completeness and accuracy.

9. Data Handling and Record keeping

9.1 Case Report Forms/ Source Data Handling

All required study data must be entered in the 21 CFR part 11 compliant eCRF created for the study. This data collection tool is a validated electronic data capture (EDC) system that contains a system-generated audit trail.

Data required according to this protocol are recorded by investigational site personnel via data entry into the internet-based EDC software system. The Investigator shall ensure that all data from participant visits are promptly entered into the eCRFs in accordance with the specific instructions given. The Investigator must sign each eCRF to verify the integrity of the data recorded. At the end of the study, all data captured electronically will be provided to the Investigator on CD ROM for archiving at the archival facility.

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated before the study starts. If a central laboratory has been selected to conduct any or all tests, all samples must be analyzed at that laboratory.

The Investigator must maintain source documents, such as laboratory reports, ECGs, consultation reports, and complete medical history and physical examination reports. All information in the eCRF must be traceable to the source documents in the participant's file. The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

9.2 Direct Access to Source Data/Documents

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the participants treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents include but are not limited to, medical history, laboratory reports, physical examination records, concomitant medications and analytical reports. It is the investigator's obligation to ensure documentation of all relevant data in the participant's file, such as medical history/concomitant diseases, date of study enrollment, visit dates, examination results, medications administered and reported adverse events.

The investigator will permit trial-related monitoring, Sponsor personnel, CRO personnel, audits, IEC/IRB review and competent authority inspection and will provide direct access to source documents. Study site personnel will enter participant data into eCRFs.

10. Quality Control and Quality Assurance

CRO will manage the study, and will be responsible for overseeing the conduct of the sites and the validity of study data. CRO will appoint suitably qualified monitors to represent the sponsor at sites and to ensure the smooth and accurate conduct of the study at the sites.

Appropriately qualified and trained staff at the site will be involved in this study. The eCRFs will be checked for completeness and plausibility by the site's investigator (manually) as well as by the monitor and data management (manually and computer-based) team. The investigator should ensure that all the trial-related duties are allocated within the research team at the site. Each of the study personnel of the study team assigned a duty must be qualified by experience and training for performing that duty. The investigator should document duty allocation by maintaining a "study personnel signature log" or "duty delegation log". Overall, the ultimate responsibility of study conduct at the clinical site lies with the Principal Investigator.

CRO will prepare a detailed monitoring plan and appoint the monitors to oversee the study conducted at each site. Monitors will conduct regular monitoring visits to ensure that the study is conducted in accordance with the protocol and ICH-GCP. Monitors will also perform adequate quality checks of the individual participant's data as per the monitoring plan. Monitoring will be performed by SOPs / manuals developed by the CRO in order to comply with GCP obligations and to ensure the international acceptability of the study data. Therefore, the investigator will make the records available to the sponsor or designee or to the sponsor upon request at reasonable times.

Data verification is required and will be done by direct comparison with source documents by cross-checking with source documents in the presence of the investigator - always giving due consideration to data protection and medical confidentiality.

Audits may be carried out by a quality assurance representative of the sponsor/CRO. The investigator will permit a representative of the CRO or the sponsor to monitor the study as frequently as necessary to determine that data recording and protocol adherence are satisfactory. The eCRFs and related documents will be reviewed in detail in accordance with the SOPs of the CRO and the sponsor and GCP regulations.

11. Ethical Considerations

11.1 Independent Ethics Committee or Institutional Review Board

Regulations require that all investigational studies be conducted under the supervision of an IEC/IRB. Clinical trial regulations and the ICH guidelines require that approval be obtained from an Ethics Committee (EC) institutional review board (IRB) before the participation of human participants in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study participants, and any other written information regarding this study to be provided to the participant or the participant's legal guardian must be approved by the IEC/IRB. Documentation of all IEC or IRB approvals and the IEC/IRB compliance with ICH harmonized tripartite guideline "ICH E6(R3): Good Clinical Practice (GCP)" will be maintained by the study site and will be available for review by the sponsor or its designee. All IEC/IRB approvals should be signed by the IEC/IRB chairman or designee and must identify the IEC/IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

PI will provide the Sponsor or CRO with documentation of Ethics Committee (EC) approval of the protocol, ICF and all documents required as per applicable regulations before the study may begin at the study sites. EC shall maintain all the study records for not less than 5 years from the date of study completion or termination of the trial. Documentation of all IEC or IRB approvals and the IEC/IRB compliance with ICH harmonized tripartite guideline "ICH E6(R3): Good Clinical Practice (GCP)" will be maintained by the study site and will be available for review by the sponsor or its designee. PI will supply documentation to the Sponsor or CRO of required EC's annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol.

The PI will promptly supply the sponsor or its designee, the IEC/IRB, and where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to participants. Similarly, the PI will submit written summaries of the study status to the EC annually, or more frequently if requested by the EC. Upon completion of the study, the PI will provide the EC with a brief report of the outcome of the study, if required.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals as specified by the IEC/IRB. The investigator must promptly supply the sponsor or its designee, the IEC/IRB, and where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to participants.

11.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

If a serious breach is detected, the sponsor or its designee will take appropriate corrective and preventative actions in response. These actions will be documented, and the regulatory authorities will be notified as appropriate.

The investigator is responsible to take appropriate action to protect a participant's life but must notify the sponsor or its designee and the medical monitor after any such event.

Amneal or its designee will comply with all regulatory requirements when reporting SAEs and urgent safety issues.

11.3 Participant Information and Consent

Written informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 will be obtained from all the participants before any study-specific procedures are carried out. In obtaining the ICF, investigator will comply with all applicable regulatory requirements, GCP and Ethical principles that have their origin in the declaration of Helsinki.

Before recruitment and enrollment, the Investigator /designee shall fully inform each prospective participant or his or her legal guardian will be given a full explanation of the study. The participant will be given ample time to read the informed consent and the investigator shall address all the queries raised by the participant. Once the investigator is assured that the participant or legal guardian understands the implications of participating in the study, the participant or legal guardian will be asked to give consent to participate in the study by signing the ICF. The investigator/ designee shall also sign the ICF. The investigator shall retain the signed original ICF and give a copy of the signed original form to the participant or legal guardian. If the ICF is revised during the study, all active participating participants must sign the revised form. The participant shall be made aware of all the risks and benefits involved in the study. Participants will also be made aware that in case of trial-related injury/death, free medical management and financial compensation will be provided to the participant / nominee.

Participants will also be informed that they are free to withdraw at any point of time during the study. The investigator is responsible for ensuring that informed consent is obtained from each participant or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of the study drug. If any institution-specific modifications to study-related

procedures are proposed or made by the study site, the consent should be reviewed by the sponsor or its designee or both before IEC/IRB submission. Once reviewed, the consent will be submitted by the investigator to his or her IEC/IRB for review and approval before the start of the study. If the ICF is revised during the study, all active participating participants must sign the revised form. Before recruitment and enrollment, each prospective participant or his or her legal guardian will be given a full explanation of the study and be allowed to read and understand the approved ICF. Once the investigator is assured that the participant or legal guardian understands the implications of participating in the study, the participant or legal guardian will be asked to give consent to participate in the study by signing the ICF. The investigator shall retain the signed original ICF and give a copy of the signed original form to the participant or legal guardian.

12. Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be participant to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IEC/IRB but will not result in protocol amendments.

12.1 Confidentiality

All evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant (or the participant's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the regulatory authorities or the IEC/IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than the performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

12.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor or their designee to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor or its designee a commitment to promptly update this information if any relevant changes occur during the investigation and for 1 year after the completion of the study.

The sponsor or its designee is not financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, the sponsor or its designee is not financially responsible for further treatment of the participant's disease.

12.3 Investigator Documentation

Before beginning the study, the investigator will be asked to comply with ICH E6(R3) C.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to the following:

- IEC/IRB approval

- Original investigator-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the investigator and each sub-investigator listed on Form FDA 1572
- Financial disclosure information to allow the sponsor or its designee to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition,the investigators must provide to the sponsor or its designee a commitment to promptly update this information if any relevant changes occur during the investigation and for 1 year after the completion of the study.
- IEC/IRB-approved informed consent, samples of study site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the participant or legal guardian
- Laboratory certifications and normal ranges for any local laboratories used by the study site

12.4 Study Conduct

The investigator agrees that the study will be conducted per the principles of ICH E6(R3). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before the enrollment of participants begins.

12.5 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs per the timeline and method outlined in the protocol (see Section 7.2.6 and Section 7.2.7). In addition, the investigator agrees to submit annual reports to the study site's IEC/IRB as appropriate.

12.6 Investigator's Final Report

Upon completion of the study, the investigator, or where applicable the institution, should provide the IEC/IRB with a summary of the study's outcome at the study site (e.g., total number of participants enrolled, study duration) and provide the sponsor or its designee with any reports required.

12.7 Records Retention

The Investigator/institution should maintain the study documents as specified in the ICH guidelines on GCP and as required by the applicable regulatory requirements. The Investigator/institution should take measures to prevent accidental or premature destruction of

these documents. Essential documents should be retained for at least 15 years from the time of initiation of the study. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor or its designee. It is the responsibility of the sponsor or its designee to inform the investigator/institution as to when these documents no longer need to be retained.

13. Study Management

13.1 Monitoring

13.1.1 Monitoring of the Study

The monitoring strategy for the study foresees a risk-based monitoring approach, in line with the relevant FDA recommendations, and will be described in detail by the study-specific risk-based Monitoring Plan. Site monitoring includes both source data review and source data verification. Site monitors perform source data review of critical procedures to ensure that the safety and rights of participants are being protected and that the study is being conducted in accordance with the currently approved protocol, any other study agreements, ICH GCP, and all applicable regulatory requirements. Site monitors perform source data verification of critical data to confirm transcription of data entered into the eCRF by authorized site personnel is accurate, complete, and verifiable from source documents.

Monitoring details describing strategy (e.g., identifying key risk indicators in operations/quality such as Risk Management, Mitigation Strategies, etc.), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (remote, or on-site monitoring) are provided in the Monitoring Plan.

The Investigator, as part of his/her responsibilities, is expected to cooperate with the Sponsor/CRO in ensuring that the study adheres to GCP requirements. The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF. The Investigator may not recruit participants into the study until such time that a visit, or with the agreement of the Sponsor, attendance at the SIV/Investigator meeting, has been made by a Sponsor/CRO monitor to conduct a detailed review of the protocol, source documents and eCRF. The Investigator shall grant direct access to original source documents and study records to the Sponsor or designee Site Monitor in order to conduct source data review, to ensure that the participants' well-being is maintained, data are being recorded adequately according to ALCOA-C principles (i.e., that they are attributable, legible, contemporaneous, original, accurate, and complete), that protocol and GCP adherence is satisfactory, and to verify accurate transcription of data to the eCRF.

The clinical monitor, as a representative of the sponsor or its designee, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and study site personnel.

All aspects of the study will be carefully monitored/ reviewed by the CRO, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

13.1.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, CRO personnel, or a regulatory agency (e.g. FDA or other regulatory agency) access to all study records. The investigator should promptly notify the sponsor, or its designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor or its designee.

13.2 Management of Protocol Amendments and Deviations

13.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the participant, will be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IEC/IRB for approval before participants can be enrolled into an amended protocol.

13.2.2 Protocol Deviations

The investigator or designee will document and explain in the participant's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study participants without prior IEC/IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IEC/IRB for review and approval, to the sponsor or its designee for agreement, and the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor or its designee and the IEC/IRB and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the participant or investigator that results in a significant, additional risk to the participant. Significant deviations can include non-adherence to inclusion or exclusion criteria, enrollment of the participant without prior sponsor approval, or nonadherence to FDA regulations or ICH GCP

guidelines, and will lead to the participant being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor during all the monitoring visits. Investigators will be notified in writing by the monitor of deviations. The IEC/IRB should be notified of relevant protocol deviations in a timely manner.

13.3 Study Termination

Although Amneal has every intention of completing the study, Amneal reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last participant completes the last visit. In the event of study discontinuation, the Sponsor /CRO will provide a prior written communication of the decision to terminate the study to the Investigator. The investigator will be responsible for informing the ethics committee about the study termination decision and following study closure activities. The ethics committee (IRB) can also terminate the study for the safety of participants and major violations of ethical considerations.

14. Financing and Insurance

With respect to any liability directly or indirectly caused by the IP in connection with this clinical trial, the sponsor assumes liability on behalf of the investigator for possible injury to the participant, provided the investigator has followed the instructions of the sponsor in accordance with this protocol and any amendments thereto, that the IP has been supplied by the Sponsor, and that the investigator has performed the clinical trial in accordance with scientific practice and currently acceptable techniques and knowledge. The sponsor's liability will be covered by liability insurance.

15. Publication Policy

All information concerning the product as well as any matter concerning the operation of Amneal Pharmaceuticals LLC, including (but not limited) to clinical indications for the drug, its formula, patent applications, basic science data and methods of manufacture and other scientific data relating to it, including procedures to conduct this trial, that have been provided by Amneal Pharmaceuticals LLC, are confidential and must remain the sole property of Amneal Pharmaceuticals LLC. The investigator agrees to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from Amneal Pharmaceuticals LLC. and CRO is obtained.

The investigator understands that the information developed in this study will be used by Amneal Pharmaceuticals LLC. in connection with the continued product development and may thus be disclosed as required to other clinical investigators or regulatory agencies.

Amneal Pharmaceuticals LLC. has full ownership of the CRO data compiled as part of the study. Any use or reproduction of any forms, protocols, quality-of-life instruments, manuals, or other documents provided by Amneal Pharmaceuticals LLC remains the property of the entity providing these documents. By signing the study protocol, the investigator agrees that the study results may be used for national and international registration, publication, and information for medical and pharmaceutical professionals by Amneal Pharmaceuticals LLC. If necessary, regulatory authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

The sponsor or its designee will prepare the clinical study reports as per applicable regulatory requirements. The sponsor or its designee will ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonized tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, the sponsor or its designee will provide the investigator with the full summary of the study results. The study results will be posted on publicly available clinical trials.

16. Reference List

1. Prescribing information TESTOSTERONE CYPIONATE injection, for intramuscular use 06/2022 https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/216318s000lbl.pdf
2. James S. Bernstein and Om P. Dhingra; A phase III, single-arm, 6-month trial of a wide-dose range oral testosterone undecanoate product; Received: 18 April 2023; revised manuscript accepted: 29 February 2024.
3. ICH Topic E 1 Population Exposure: The Extent of Population Exposure to Assess Clinical Safety- June 1995.
4. Investigator Brochure or Prescribing information of Testosterone Cypionate (50 mg, 75 mg and 100 mg) auto-injector for subcutaneous use (Amneal Pharmaceuticals, LLC).
5. Heinemann LA, Saad F, Zimmermann T, Novak A, Myon E, Badia X, Potthoff P, T'Sjoen G, Pöllänen P, Goncharow NP, Kim S, Giroudet C. The Aging Males' Symptoms (AMS) scale: update and compilation of international versions. Health Qual Life Outcomes. 2003 May 1;1:15. doi: 10.1186/1477-7525-1-15. PMID: 12747807; PMCID: PMC155679.
6. ICH-GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R3)= 06 January 2025.
7. USFDA-Bioanalytical Method Validation Guidance for Industry- May 2018
8. ICH M10 on bioanalytical method validation - Scientific guideline- 21/01/2023.

17. Appendices

17.1 Appendix: Table of Study Assessment and Schedule of Events

Study Assessments and Schedule of Events of TREATMENT PHASE

Study phase	**Screening phase (V1)**					**Treatment Phase**											
V: Visit, Q: Qualifying & Wk: Week	**Initial screen**	**W O**	**TT Q-1a**	**TT Q-1b**	**TT Q-1c**	**Wk 1 (V2)**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6 (V3)**	**Wk 7 (V4)**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12 (V5)**
Study day [$]	**-28 to -1 (approximately)**					**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**
Informed Consent	X																
Medical/surgical history	X																
Medication history	X																
Age, ethnicity, race, gender	X																
Height [D], weight and BMI	X																X
Physical examination (PE) including digital rectal exam (DRE)	X																X[(OP)]
Housing / Domicile at site (10.00 hour before and up to 24 h post dose)-subject to infrastructure [Week 1 & 6 for 45 P (45 participants)]						X (for 45 P)					X (for 45 P)						X
Symptom based PE						X					X						
Vital signs [E]	X		X	X	X (if applicable)	X	X (for 45 P)				X	X					X
Clinical laboratory assessments [F]																	
• Prostate Specific Antigen (PSA) & Endocrine function [F]	X					X											X
• Coagulation Tests	X					X											X
• Serology [F]	X																
• Qualifying total testosterone (TT) levels			X	X	X (if required)												
• Additional sample for qualifying TT at BL	X		X	X	X (if required)												
• Urinalysis [F]	X					X											X
• Urine Drug screen	X					X											X
• Biochemistry [F]	X					X											X
• Hematology [F]	X					X											X
• HbA1c for diabetic patients	X					X											X
• Albumin, SHBG	X					X					X						X
ECG	X					X											X
Verification of all eligibility criteria						X											
Register participants in the interactive web response system	X																

Study phase	**Screening phase (V1)**					**Treatment Phase**										
V: Visit, Q: Qualifying & Wk: Week	**Initial screen**	**WO**	**TT Q-1a**	**TT Q-1b**	**TT Q-1c**	**Wk 1 (V2)**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6 (V3)**	**Wk 7 (V4)**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12 (V5)**
Study day [$]	**-28 to -1 (approximately)**					**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**
(IWRS)																	
IP dispensing via IWRS						X						X					
Issue of study drug						X						X					
Diary issue for compliance to dose						X											
Recording of dose administration in the diary by participant							X	X	X	X	X	X	X	X	X	X	X
Dose administration by study staff at site [G]						X											
Injection site assessment [H]						X	X				X	X					X
Continuous Ambulatory Blood Pressure Monitoring ABPM (from 0.5 hours pre-dose to 24 hours post-dose) Baseline ABPM should be completed before dosing on day 1						X (week -1 to day 1)											X
TT trough Blood sample (Central /Clinical Lab) [I]											X (1)						X (1)
PK profile blood collection (TT, DHT, DHTC, E2 and TC) [FPK] for 45 P (No. of samples)						X(9)	X(1)		X (1)	X (1)	X (10)	X(1)		X(1)	X(1)	X(1)	X (12)
PK profile blood collection (TT, DHT, DHTC, E2 and TC) [FPK] rest the of the participants (No. of samples)						X(1)			X(1)	X(1)	X(1)			X(1)	X(1)	X(1)	X (12)
Titrate dose via IWRS, if required												X					
IP accountability and compliance (diary)											X						X
Autoinjector device training and assessment of self- administration essential tasks by study staff						X											
Self-administration of study drug by patient							X	X	X	X	X	X	X	X	X	X	X
Diary issue for glucose to diabetic patients						X											
Glucose monitoring (self-monitoring once weekly between day 2- 7) for diabetic patients						X	X	X	X	X	X	X	X	X	X	X	X

Study phase	**Screening phase (V1)**					**Treatment Phase**										
V: Visit, Q: Qualifying & Wk: Week	**Initial screen**	**W O**	**TT Q-1a**	**TT Q-1b**	**TT Q-1c**	**Wk 1 (V2)**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6 (V3)**	**Wk 7 (V4)**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12 (V5)**
Study day [$]	**-28 to -1 (approximately)**					**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**
Issue of Glucometer and /or strips for diabetic patients						X					X						
Diary review for or glucose (diabetic patients)											X						X
I-PSS	X					X											
Aging Males' Symptoms (AMS) (applicable for ≥ 40 years)						X											
Patient Global Impression of Change (PGI-C)						X											
C-SSRS, HDRS, SIAQ, SF-36, Assessment of Essential Tasks Questionnaire						X											
Concomitant medication review during visit	X	X	X	X	X	X					X	X					X
Adverse event collection/monitoring	X	X	X	X	X	X					X	X					X
Meal [J]						X for 45 P					X for 45 P						X

Note: 45P: 45 Participants

[$]: **Window period**

- All scheduled study activities should be performed on the designated study days. However, a visit window of ±2 days will be permitted for weekly dose administration and the corresponding study assessments for week 2 onward, except for the Week 12 dose administration, full PK sampling, and associated assessments.
- The ±2-day visit window is not applicable to Week 12 dose administration for any subject. The Week 12 dose must be administered on the same weekday as the Week 1 dose administration.
- For the subset of 45 subjects participating in the intensive PK sampling schedule at Weeks 1 and 6, the ±2-day visit window is applicable only to Weeks 2, 3, 4, 5, and Weeks 7, 8, 9, 10, and 11. The Week 6 visit, including dose administration, full PK sampling, and all associated assessments, must be conducted on the scheduled study day without any visit window.
- Whenever the ±2-day visit window is used for any weekly visit, subsequent weekly dose administrations must be rescheduled to the original Week 1 dosing weekday. The visit window does not permanently shift the dosing schedule.

Dose	Date of administration (Week day)
Week 1	Actual: 03/Aug/2026 (Monday)
Week 4	Schedule: 24/Aug/2026 (Monday)
Example 1, if window period of +2 days is used for week 4	
Week 4	Actual: 26/Aug/2026 (Wednesday)
Week 5	Schedule: 31/Aug/2026 (Monday) **and not 02/Sep/2026 (Wednesday)**
Example 2, if window period of -2 days is used for week 4	
Week 4	Actual: 22/Aug/2026 (Saturday)
Week 5	Schedule: 31/Aug/2026 (Monday) **and not 29/Sep/2026 (Saturday)**

- A visit window of ±2 days will also be permitted for C_{trough} sample required for dose titration at Week 6, 18, 24, and scheduled visits thereafter, and PK steady-state sample collection scheduled at Weeks 4, 5, 6 (except for the 45 subjects undergoing full PK sampling), 9, 10, and week 11.
- The visit window for PK sample collection and other scheduled study assessments will remain the same and will be referenced to the actual dosing time at the respective visit.

WO: Washout period will be dependent on participant's testosterone therapy at time of screening. participants who will be naïve to treatment or who will discontinue testosterone therapy with adequate WO (washout) before the initial screen, will be permitted to proceed to TT Qualification Visit **(TT Qual 1)**. And this visit will be combined with the initial screening visit.

- Oral, buccal, or transdermal testosterone regimen (participants will undergo 2-week washout prior to visit 1
- Currently treated with a stable IM testosterone regimen (dose and interval) for a minimum of 3 consecutive doses (dose must be 50 mg to 400 mg administered at intervals no greater than every 4 weeks) (participants will undergo 5-week washout prior to visit 1)
- Completed washout of treatment prior to screening (i.e., 2-week washout for buccal or transdermal, or 5-week washout of IM testosterone or end of dosing interval for Testopel participants i.e. at least 12-weeks from the initiation, prior to visit 1). Participants who have completed washout of treatment prior to screening will follow the same procedures as participants who are treatment-naïve

TT Qual 1a/1b/1c: The TT Qual1a visit will complete as soon as the washout period completed. All TT Qual visits will be performed between 07:30 AM - 10:00 AM on two separate days at least 72 hours apart during screening period. One repeat total T concentration will be allowed if 1 of the 2 morning total T concentrations is ≥300 ng/dL
A minimum of 2 TT <300 ng/dL will be required for study participation. If 1 of the TT values from TT Qual 1a or Qual 1b visits was ≥ 300ng/dL, 1 reset will be allowed at TT Qual1c, if 1 of the 2 morning total T concentrations is ≥300 ng/dL.

[D:] Height will be calculated only at screening.

[E]: Vitals (Axillary body temperature, Pulse Rate, Respiratory Rate, Blood Pressure) will be examined
For 45 participants with week 1, 6 and week 12 full PK sampling: in screening and TT qualification visits, in Week 1, week 6 and Week 12 at 0.00 (pre-dose), 1.00, 3.00, 6.00, 10.00, 24.00 post dose (Within ± 45 minutes variation) and at the time of each ambulatory PK blood sample collection of week 1, week 6 and week 12 (± 2 h).

For the rest of the participants (only week 12 full sampling): in screening and TT qualification visits, pre-dose of Week 1, week 6 and week 7, and in Week 12 at 0.00 (pre-dose), 1.00, 3.00, 6.00, 10.00, 24.00 post dose (Within ± 45 minutes variation) and at the time of each ambulatory PK blood sample collection of week 12 (± 2 h).

[F]: Participants will fast a minimum of 8 hours prior to all clinical laboratory assessments including PSA, endocrine function, and qualifying TT blood sampling. Refer clinical laboratory tests table. section 7.4.
During the screening phase, to reduce screen failures, before conducting comprehensive all the clinical laboratory assessments, all the participants may undergo at least one qualifying serum testosterone concentration measurements to confirm hypogonadal status, along with HbA1c and PSA evaluation. Participants meeting this preliminary study requirement, may then proceed to comprehensive clinical laboratory assessments as per the protocol

[G:] Investigational Product Dispensing and Administration schedule: Participant will self-administer this study drug from week 2 to week 12. The study medication will be self-administered subcutaneously on the same day of each week and at approximately the same time (7:00 am ± 2hrs) to ensure consistent dosing for Pharmacokinetic (PK) Analysis.
When dose administration coincides with a study visit (Weeks 6, 7 and 12), the participant will administer the dose at the clinical study site, allowing coordination of study evaluations and assessments that are timed relative to dose administration.

Full PK profile (FPK):

For 45 participants at week 1, week 6 and week 12 and details are as follows		
Week	No. of Samples	Sampling schedule
1 (full PK)	10	0.00 (pre-dose sample), 0.50, 3.00, 6.00, 9.00, 12.00, 24.00, 48.00, 72.00, and 168.00* hours post-dose in plain vacutainers. *:Corresponds to Day 1 of Week 2.
6 (full PK)	11	0.00 (pre-dose samples), 0.50, 3.00, 6.00, 9.00, 12.00, 24.00, 48.00, 72.00, 144.00, and 168.00* hours post-dose in plain vacutainers. *:Corresponds to Day 1 of Week 7
12 (pivotal-full PK)	13	0.00 (pre-dose samples), 3.00, 6.00, 9.00, 12.00, 24.00, 36.00, 48.00, 72.00, 96.00, 120.00, 144.00, and 168.00* hours post-dose in plain vacutainers. *: Corresponds to Day 1 of Week 13
4, 5, 9, 10 and 11 (steady-state)	5	Before dose administration

For the rest of the participants full PK sampling will be performed at week 12 only and details are as follows.		
Week	No. of Samples	Sampling schedule
1, 4, 5, 6, 9, 10 and 11 (Pre-dose / steady-state)	7	Before dose administration
12 (full PK)	13	0.00 (pre-dose samples), 3.00, 6.00, 9.00, 12.00, 24.00, 36.00, 48.00, 72.00, 96.00, 120.00, 144.00, and 168.00* hours post-dose in plain vacutainers. *:Corresponds to Day 1 of Week 13

Window period of -15 (fifteen)minutes for 0.00 hours pre-dose samples.
Up to 24.00 h post-dose PK samples will be collected during housing period at study site with window period of ± 5 minutes and rest all (up to 168.00 h) are collected as ambulatory PK blood samples (± 2 h)]. For clinical sites that do not have the infrastructure to accommodate overnight stays, subjects may instead return to their homes and will be instructed to return to the site the following day for scheduled study procedures.
Note: If the participant is unable to come to the site on the scheduled ambulatory PK sampling day, designated study personnel may visit the participant's home for collection.
These will be analysed at Bioanalytical Laboratory.

[H:] Injection site assessments (ISA) completed as per below schedule. Unscheduled ISA may be completed as deemed necessary by the investigator.
Pain will be assessed by visual analogue scale (VAS).

Participants	ISA number of time points	Week and schedule
For all Participants	11	Week 1: before dosing and after dosing at 0.50, 01.00 h Week 6: after dosing at 0.50, 01.00 h Week 7: after dosing at 0.50, 01.00 h Week 12: before dosing and after dosing at 0.50, 01.00 and 24.00 h
Additional Only for 45 participants who are with week 1 and week 6 full PK sampling	5	Week 1: Ater dosing at 24.00, 36.00 and 48.00 h Week 2: After dosing at 0.50 and 1.00 hours
Window period- Pre-dose:30 minutes, for 0.50 and 1.00 h: ± 15 minutes, for 24.00: ± 30 minutes, for 36.00 and 48.00 h: ± 2 h		

[I]: C_{trough} blood sample (Central lab) must be obtained before 15 mins autoinjector dose administration.

- On week 6, C_{trough} sampling will be done. On week 7, dose will be titrated based on C_{trough} concentration of week 6.
- On week 12, C_{trough} sampling will be done. On week 13, dose will be titrated based on C_{trough} concentration of week 12.

[J:] Meal will be provided at appropriate intervals during the housing period after study drug administration.
[OP]: DRE will be performed if investigator feels necessary

Study Assessments and Schedule of Events of TREATMENT PHASE AND CONTINUED SAFETY FOLOWUP

Study phase	**Extended Treatment Phase and Continued Safety Follow Up**												**Follow-up visit (V18)**
V: Visit, & Wk: Week	**Wk 13 (V6)**	**Wk 18 (V7)**	**Wk 19 (V8)**	**Wk 24 (V9)**	**Wk 25 (V10)**	**Wk 30 (V11)**	**Wk 31 (V12)**	**Wk 36 (V13)**	**Wk 37 (V14)**	**Wk 42 (V15)**	**Wk 43 (V16)**	**Wk 52 (EOT / ET) (V17)**	
Study day [$]	**85**	**120**	**127**	**162**	**169**	**204**	**211**	**246**	**253**	**288**	**295**	**358**	**7 -14 days**
Physical examination (PE) including DRE				X(OP)				X(OP)				X(OP)	
Symptom based PE		X				X				X			
Weight and BMI (using screening height)				X				X				X	
Vital signs (Axillary body temperature, Pulse Rate, Blood Pressure, Respiratory rate)	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory assessments [F]													
• Hematology [F]				X				X				X	
• Biochemistry [F]				X				X				X	
• Urinalysis [F]				X				X				X	
• Endocrine function assessment & PSA, Coagulation [F]				X				X				X	
• HbA1c for diabetic patients				X				X				X	
• TT C_{trough} Blood sample (Central) [L]		X		X		X		X		X		X	
• TT C_{trough} Blood sample at BL [L]		X		X		X		X		X			
• Albumin, SHBG		X		X		X		X		X		X	
ECG				X				X				X	
Urine drug screen				X				X				X	
IP dispensing via IWRS	X		X		X		X		X		X		
PK sample of week 12 for all participants	X (1)												
Dose administration (self)	X	X	X	X	X	X	X	X	X	X	X	X	
Recording self-drug administration in diary	X	X	X	X	X	X	X	X	X	X	X	X	
Injection site assessment [K]	X	X	X	X	X	X	X	X	X	X	X	X	
Titrate dose via IWRS, if required	X		X		X		X		X		X		
IP accountability and compliance through diary		X		X		X		X		X		X	
I-PSS				X								X	
Aging Males' Symptoms (AMS) (applicable for ≥ 40 years)				X								X	

Study phase	**Extended Treatment Phase and Continued Safety Follow Up**												**Follow-up visit (V18)**
V: Visit, & Wk: Week	**Wk 13 (V6)**	**Wk 18 (V7)**	**Wk 19 (V8)**	**Wk 24 (V9)**	**Wk 25 (V10)**	**Wk 30 (V11)**	**Wk 31 (V12)**	**Wk 36 (V13)**	**Wk 37 (V14)**	**Wk 42 (V15)**	**Wk 43 (V16)**	**Wk 52 (EOT / ET) (V17)**	
Study day [$]	**85**	**120**	**127**	**162**	**169**	**204**	**211**	**246**	**253**	**288**	**295**	**358**	**7 -14 days**
Patient Global Impression of Change (PGI-C)				X								X	
C-SSRS, HDRS, SIAQ, SF-36, Assessment of Essential Tasks Questionnaire				X								X	
Glucose monitoring (self-monitoring once weekly) for diabetic patients	X	X	X	X	X	X	X	X	X	X	X	X	
Issue of Glucometer and strips for diabetic patients	X		X		X		X		X		X		
Issue of study drugs	X		X		X		X		X		X		
Continuous Ambulatory Blood Pressure Monitoring (from 0.5 hours pre-dose to 24 hours post-dose) ABPM				X								X	
Diary review for compliance to glucose monitoring		X		X		X		X		X		X	
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event collection / monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X
Register completion in IWRS													X

Note:

- ✓ Study drug will be self-administered subcutaneously once each week on the same day of each week and approximately the same time (7:00 am ± 2hrs).
- ✓ When dose administration coincides with a study visit (Weeks 13, 18, 19, 24, 30, 31, 36, 37, 42, 43 and 52), the participant will self-administer the dose at the clinical study site, allowing coordination of study evaluations and assessments that are timed relative to dose administration.
- ✓ Day 8 of Week 12 corresponds to the week 13 visit for the treatment phase.

[K:] ISA will be performed at 0.5 and 1 (window period of ± 15 minutes) hour after dose administration in week 13, 19, 24, 25, 30, 31, 36, 37, 42, 43 and 53, if reactions is observed-will be evaluated 24- hours after dose administration during an unscheduled visit. Unscheduled ISA may be completed as deemed necessary by the investigator. Pain will be assessed by VAS.

[L:] C_{trough} blood sample must be obtained before 15 mins autoinjector dose administration.

- On week 12, 18, 24, 30, 36, and week 42 C_{trough} sampling will be done. On week 13, 19, 25, 31, 37, and week 43 dose will be titrated based on C_{trough} concentration of week 12, 18, 24, 30, 36, and week 42 and the IP will be dispensed for up to 6 weeks at respective planned dose titration visits.

- On week 52, C_{trough} sampling will be done.

End of study assessments completed at week 52 or at the point the participant withdraws from the study (Early termination/ ET). Follow-up visit should be completed 7-14 days after completion of the final assessments.

[OP]: DRE will be performed if investigator feels necessary

17.2 APPENDIX: CHANGE HISTORY

Current Version No.	Supersedes, Effective Date	Changes Made
4	3, 22/Jul/2026	1. Provision for rescreening is included as per recommended by the Investigator in section 1 and 4.1.
3	2, 04/Jun/2026	1. Window period applicability and following week dose administration for weekly dose administration is elaborated for better clarity with the following information. • The ±2-day visit window is not applicable to Week 12 dose administration for any subject. The Week 12 dose must be administered on the same weekday as the Week 1 dose administration. • For the subset of 45 subjects participating in the intensive PK sampling schedule at Weeks 1 and 6, the ±2-day visit window is applicable only to Weeks 2, 3, 4, 5, and Weeks 7, 8, 9, 10, and 11. The Week 6 visit, including dose administration, full PK sampling, and all associated assessments, must be conducted on the scheduled study day without any visit window. • Whenever the ±2-day visit window is used for any weekly visit, subsequent weekly dose administrations must be rescheduled to the original Week 1 dosing weekday. The visit window does not permanently shift the dosing schedule. • The visit window for PK sample collection and other scheduled study assessments will remain the same and will be referenced to the actual dosing time at the respective visit. 2. Performing Digital rectal examination at specified intervals after first dose administration is made investigator's discretion as recommended by investigators based in the clinical practice. 3. The Aging Males' Symptoms (AMS) questionnaire is a three-dimensional instrument designed to assess the severity of aging-related symptoms in men. It was originally validated in men aged 40 to 69 years and has been widely used in older men. However, current evidence regarding its use in men younger than 40 years remains limited. Moreover, higher specificity for predicting total testosterone levels has been reported in men older than 65 years. Based on the current evidence, AMS questionnaire will be applied only to participants aged 40 years or older at all protocol-specified time points for AMS assessment. 4. Blood loss section text is updated as table for better clarity, and correction of minor typographical errors 5. Minor typographical and editorial corrections are made throughout the protocol.
2	1, 24/Apr/2026	1. Study title is updated with primary evaluation assessment periods and with single-blind study based on the study objective and monitoring purpose, updated throughout the protocol. 2. Alternative procedure is included where non-feasibility of housing at some clinical site's due infrastructure limitations. 3. The frequency of monitoring patient related outcomes / assessments (PROs) is modified to collect post-baseline at week 24 and scheduled visits thereafter instead of every 12 weeks. 4. 36-Item Short Form Survey Instrument (SF-36) Questionnaire is included at visit 2 (week 1), visit 9 (week 24), and scheduled visits thereafter and in all applicable sections throughout the protocol, replaced with Psychosexual Daily Questionnaire (PDQ) and Pittsburgh Sleep Quality Index (PSQI). 5. Window period for weekly dose administration, scheduled visits and ABPM is included. 6. Study inclusion and exclusion criteria is slightly modified throughout the protocol. 7. The safety assessments frequency (ECG, Clinical laboratory assessment of Endocrine function, PSA, Biochemistry, Coagulation test, Hematology, Urine analysis, and for diabetic patients-HbA1c) is modified to every 12 weeks instead of every 6 weeks. 8. Sample size from 80-120 to 80-140 and expected study completers from 60-100 to 60-120 considering the long-term duration.

		9. Albumin and SHBG lab tests will be performed at screening and when serum TT is collected at week 6, 12, 18, 24, and scheduled visits thereafter. 10. Minor typographical corrections are corrected. 11. PK sampling schedule is updated.
1	None	Not applicable.