SAP MODULE 1 – DETAILED STATISTICAL METHODOLOGY

Protocol No. EN3000-101 Amendment 2: September 15, 2020

AN OPEN-LABEL, RANDOMIZED, PARALLEL-GROUP, THREE TREATMENT ARM, MULTICENTER STUDY ON HYPOGONADAL MALES TO EVALUATE THE EFFECT ON 24-HOUR AMBULATORY BLOOD PRESSURE AFTER 16-WEEK CONTINUOUS TREATMENT WITH MARKETED TESTOSTERONE PRODUCTS

Version 2.0

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ABPM	Ambulatory blood pressure monitoring
AE	Adverse event
ALT	Alanine aminotransferase
AM	ante meridiem
AR (1)	Auto-regressive (1)
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BP	Blood pressure
BPH	Benign prostatic hyperplasia
bpm	Beats per minute
BMI	Body Mass Index
brpm	Breaths per minute
CFR	Code of Federal Regulations
CI	Confidence interval
cm	centimeter
CO_2	Carbon dioxide
CYP3A	cytochrome P450 3A
DBP	Diastolic blood pressure
DMP	Data Management Plan
DRE	Digital rectal examination
ECG	Electrocardiogram
eCRF	Electronic case report form
EoS	End-of-study
ET	Early termination
FAS	Full analysis set
FDA	Food and Drug Administration
GGT	Gamma-glutamyl transferase
HR	Heart rate
IEC	Independent ethics committee
IM	Intramuscular
IPSS	International Prostate Symptom Score
IRB	Institutional review board

Abbreviation	Definition
IRT	Interactive response technology
ITT	Intent-to-Treat
kg	kilogram
MAP	Mean arterial pressure
MAR	Missing at random
MCAR	Missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
mm Hg	millimeter of mercury
MMRM	Mixed Model Repeated Measures
PCI	Potentially clinically important
PI	Prescribing information
PP	Pulse pressure
PSA	Prostate-specific antigen
PT	Preferred term
REMS	Risk evaluation and mitigation strategies
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SoA	Schedule of activities
SOC	System organ class
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TOEPH	Heterogeneous Toeplitz
ULN	upper limit of normal
UN	Unstructured
WBC	White blood cell
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the analysis that will be performed to evaluate the effect on 24-hour ambulatory blood pressure after 16 weeks continuous treatment with marketed testosterone products on hypogonadal males.

The general information about the study is detailed in the EN3000-101 protocol, original protocol dated November 17, 2019, Amendment 1 dated March 19, 2020, and Amendment 2 dated September 15, 2020 (1).

2. STUDY OBJECTIVES

The study objectives and corresponding endpoints are outlined in Table 1 below.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the change from baseline in mean 24-hour systolic blood pressure (SBP) after 16 weeks of continuous treatment with study drug as indicated by the prescribing information (PI).	• Mean change from baseline to end-of-study (EoS) in 24-hour average systolic ambulatory blood pressure (BP).
Secondary	
• To assess the safety of 16 weeks of continuous treatment with study drug as indicated by PI.	• Mean change from baseline in 24-hour average and time windows of interest in mean arterial pressure (MAP), SBP, diastolic blood pressure (DBP), pulse pressure (PP), and heart rate (HR) obtained during treatment. • Change from baseline over time (hourly average) by nominal clock time and time after dose in MAP, SBP, DBP, PP, and HR. • Percent of subjects with new antihypertensive medications. • Percent of subjects with dose increases in antihypertensive medications.

3. STUDY DESIGN AND MEASURES

3.1. Study Design

This is a Phase 4, open-label, randomized, parallel-group, 3 treatment-arm, multicenter study on hypogonadal males to evaluate the effect on 24-hour ambulatory blood pressure after 16 weeks of continuous treatment with marketed testosterone products.

The study will enroll a total of approximately 729 hypogonadal males with controlled hypertension and without hypertension across the 3 treatment arms. The study will consist of a Screening Phase (Day -28 to -2), followed by a 24-hour ambulatory blood pressure monitoring (ABPM) phase (Baseline Phase, Day -1 to 2), Treatment Phase (Day 2 to 100) and ABPM at the EoS visits (Day 106 to 115). Table 2 and Table 3 present the details of visit information. It can be seen that event days are different between AVEED® (testosterone undecanoate) injection and TESTIM® (testosterone gel)/FORTESTA® (testosterone) gel treatment.

The subjects will be randomly assigned to 1 of 3 treatment arms after a valid 24-hour ABPM session (baseline) has been confirmed.

Subjects who started this study prior to a COVID-19 interruption will be allowed to continue in the study and complete all remaining assessments, if willing to do so in accordance with the scheduling outlined in Protocol Section 1.2.

A subject who does not meet all of the eligibility criteria and is considered a screen failure may be rescreened once rescreening related procedures to the study treatment must not exceed 28 days.

3.1.1. Screening Phase (Day -28 to -2)

Screening will take place on multiple days between Day -28 and Day -2. Each subject's eligibility will be evaluated during screening. Subjects found eligible will be instructed to return to the study center on Day -1 for further activities as per schedule of activities (SoA).

A subject who does not meet all the eligibility criteria and is considered a screen failure will be rescreened once. If a subject rescreens within 30 days of their original screening date, assessments from the initial screening period will be used if they are valid and within protocol entry criteria. Any abnormal assessments will be repeated. The period from the start of rescreening related procedures to the study treatment should not exceed 28 days.

3.1.2. Baseline Phase (Day -1 to 2)

Blood samples will be collected on Day -1 for a baseline serum testosterone assessment (day before ABPM). All eligible subjects will come to the study center on Day 1 for ABPM. A 24-hour ambulatory blood pressure recorder machine will be attached to the subject's arm, at bicep level. The machine will be set to measure BP every 30 minutes for the next 24 hours.

Baseline BP will be analyzed (systolic and diastolic means) for the overall 24-hour period, daytime (from waking up to bedtime) and night-time (from retiring to bed until waking) for each subject. The 24-hour ambulatory blood pressure recorder machine must be returned to the study site by the subject on the following day (Day 2). The subject will use the same device at both the Day 1 and as applicable, the EoS or Early Termination (ET) visit.

In order to receive study drug on Day 2, the investigator (or qualified designee) must review and consider the baseline 24-hour ABPM as valid. If a subject does not have a valid ABPM session (defined as ≥ 70% of expected measurements including 20 valid awake [0900-2100 h] and 7 valid sleep [0100-0600 h] measurements) at baseline due to device error (including displacement of cuff or likewise), the ABPM session will be repeated once in order to obtain a valid ABPM session. In case of repeat ABPM session, there will be a shift in study days to account for a repeat ABPM at baseline and randomization will be considered Study Day 2.

3.1.3. Treatment Phase

After baseline ABPM is complete (Day 2) and the investigator confirmed the reading to be valid, each subject will be randomized to one of the 3 treatment arms:

- Testosterone undecanoate injection (AVEED)
- Testosterone gel (FORTESTA)
- Testosterone gel (TESTIM)

3.1.3.1. TESTIM and FORTESTA Treatment Arm (Day 2 to 97)

FORTESTA and TESTIM subjects will be administered the study drug on Day 2. Subjects will continue to topically apply/administer FORTESTA or TESTIM daily as instructed according to the approved PI.

Subjects will be allowed up to 4 treatment follow-up visits to the study center at Days 16, 37, 67, and 97 (± 3 days) for FORTESTA and TESTIM. Additional visits may occur outside this window as Unscheduled Visits.

Blood samples will be collected at these treatment follow-up visits to calculate the serum testosterone level (not applicable to AVEED). The daily dose of the study drug will be titrated for each subject, according to approved dosage and administration instructions (Package Insert), until the circulating testosterone concentrations of the subject reaches normal concentrations (300-1000 ng/dL). The timing of blood sample collection will occur 2 hours prior to TESTIM treatment and 2 hours after FORTESTA treatment, as described in the respective PIs.

The investigator will be instructed to customize and schedule the treatment follow-up visits (and study drug dispensation) of each subject according to the study drug characteristics in order to facilitate proper dose titration. Once the daily required dose is fixed, subjects will be instructed to continue the same dose until they complete the study.

3.1.3.2. AVEED Treatment Arm (Day 2 to 100)

AVEED subjects will receive an intramuscular injection on Day 2, Day 30, and Day 100 (± 3 days).

Unscheduled visits may occur as necessary for the AVEED subjects.

3.1.4. Ambulatory Blood Pressure Monitoring (End of Study)

3.1.4.1. TESTIM and FORTESTA Treatment Arm (Day 113 to 115)

Subjects will be instructed to visit the study center on Day 113 (± 3 days) for serum testosterone draw, again on Day 114 to be fitted with the ABPM device to measure BP every 30 minutes for the next 24 hours, and on Day 115 to return the device. If a subject does not have a valid ABPM session at the end of study visit, the ABPM session may be repeated once in order to obtain a valid ABPM session.

Subjects will apply the study drug as usual at home before the Day 114 visit and will complete the other EoS assessments as listed in the TESTIM and FORTESTA SoA.

3.1.4.2. AVEED Treatment Arm (Day 106 to 108)

AVEED subjects will be instructed to visit the study center on Day 106 (± 3 days) for a serum testosterone draw. Subjects will return to the study center on Day 107 to be fitted with the ABPM device to measure BP every 30 minutes for the next 24 hours in addition to completing the other assessments as listed in the AVEED SoA, and on Day 108 to return the device. If a subject does not have a valid ABPM session at the end of study visit, the ABPM session may be repeated once in order to obtain a valid ABPM session.

If a subject is terminated early, an ET visit will be scheduled and efforts will be taken to collect his 12-lead ECG, blood samples for clinical laboratory tests (including serum testosterone on the day prior to ABPM) and 24-hour ABPM data.

3.1.4.3. End-of-Study Definition

A subject is considered to have completed the study if the subject has completed the 2-day EoS visit and required assessments at this visit.

3.1.5. Study Duration

The duration of the study from first subject first visit to last subject last visit will depend on the ability of the sites to identify and enroll eligible subjects. The entire study is expected to require approximately 2 years to complete.

3.1.6. Schedule of Activities

Table 2 and Table 3 below describe the schedule of activities performed during Screening Phase, Baseline Phase, Treatment follow-up and EoS/ET visits.

Table 2: Schedule of Activities – TESTIM and FORTESTA

Procedures	Screening Phase Day -28 to -2	Baseline			Treatment Follow-up Visits[a]	End-of-Study/Early Termination (± 3 days)		
		Day -1	Visit 1 Day 1	Return Visit Day 2	Visits 2a to 2d[b] Days 16, 37, 67, and 97	Day 113	EoS Visit Day 114	Return Visit Day 115
Informed consent	X							
Inclusion/exclusion	X		X					
Medical history including previous treatments	X							
Prior/concomitant medications	X	X	X	X	X	X	X	X
Physical examination	X						X	
Height	X							
Weight	X		X		X		X	
Vital signs (temperature, HR, BP & RR)[c]	X		X	X	X		X	X
12-lead ECG	X						X	
International Prostate Symptom Score (IPSS)[d]	X							
Digital rectal examination of the prostate	X							
Alcohol and tobacco screen	X							
Clinical laboratory[e]	X							

Procedures	Screening Phase Day -28 to -2	Baseline			Treatment Follow-up Visits[a]	End-of-Study/Early Termination (± 3 days)		
		Day -1	Visit 1 Day 1	Return Visit Day 2	Visits 2a to 2d[b] Days 16, 37, 67, and 97	Day 113	EoS Visit Day 114	Return Visit Day 115
Serum testosterone	X[f]	X			X[g]	X[g]		
24-hour ABPM			X[h]				X[h]	
Confirm valid ABPM session				X				X

Table 2: Schedule of Activities – TESTIM and FORTESTA (Continued)

Procedures	Screening Phase Day -28 to -2	Baseline			Treatment Follow-up Visits[a]	End-of-Study/Early Termination (± 3 days)		
		Day -1	Visit 1 Day 1	Return Visit Day 2	Visits 2a to 2d[b] Days 16, 37, 67, and 97	Day 113	EoS Visit Day 114	Return Visit Day 115
AEs/SAEs	X	X	X	X	X	X	X	X
TREATMENT								
Randomization[j]				X				
Dispense Study Drug[k]				X	X			
Collect Study Drug					X			X

Procedures	Screening Phase Day -28 to -2	Baseline			Treatment Follow-up Visits[a]	End-of-Study/Early Termination (± 3 days)		
		Day -1	Visit 1 Day 1	Return Visit Day 2	Visits 2a to 2d[b] Days 16, 37, 67, and 97	Day 113	EoS Visit Day 114	Return Visit Day 115
AEs/SAEs	X	X	X	X	X	X	X	X
Study Drug Compliance Check and Discussion					X			X

[a] Treatment follow-up visits are for checking serum testosterone levels and titrating dose accordingly. For subjects receiving FORTESTA, if further titration is required after Follow-up Visit on Day 37, the investigator should refer to the PI for information on subsequent follow-up visits. However, in the event additional visits are necessary, they may occur as Unscheduled Visits.

[b] Window of ± 3 days are allowed.

[c] Temperature, heart rate (HR) and respiratory rate (RR) will be captured. BP will be measured, using a sphygmomanometer, at all office visits. Subjects will be seated on a chair with back rest, resting the flexed dominant arm on a flat surface so that the upper arm is at heart level. Subjects with BP > 140/90 mm Hg should be excluded from the study. Site personnel will ensure that the same arm and cuff size will be used. Vital signs taken will include SBP and DBP, pulse rate, respiratory rate, and body temperature. The results, date, and time for all vital sign assessments will be recorded.

[d] International Prostate Symptom Score (IPSS) ≥ 19.

[e] Includes tests for hematology, biochemistry, serum prostate-specific antigen (PSA), and urine analysis.

[f] Two blood samples will be obtained for serum testosterone, at 10 AM (± 2 hours) on 2 separate occasions spaced at least 48 hours apart (± 1 hour).

[g] On the TESTIM treatment arm a blood sample will be collected from subjects 2 hours predose, and on the FORTESTA treatment arm a blood sample will be collected from subjects 2 hours postdose.

[h] Onsite device activation.

[i] If a subject does not have a valid ABPM session (defined as ≥ 70% of expected measurements including 20 valid awake [0900-2100 h] and 7 valid sleep [0100-0600 h] measurements) at baseline or at the end of study visit the ABPM session can be re-done.

[j] A valid ABPM must be confirmed prior to a subject being randomized.

[k] The appropriate amount of study drug will be dispensed to each subject to last until the next follow-up visit, with instructions for administration. However, if up titration is needed, subjects may need to return to the clinic between scheduled follow-up visits for additional drug supply.

Table 3: Study Schedule of Activities – AVEED (Testosterone Undecanoate Injection)

Procedures	Screening Phase Day -28 to -2	Baseline			Treatment Visits (± 3 days)		End-of-Study/Early Termination (± 3 days)		
		Day -1	Visit 1 Day 1	Return Visit Day 2	Study Visit Day 30	Study Visit Day 100	Day 106	EoS Visit Day 107	Return Visit Day 108
Informed consent	X								
Inclusion/exclusion	X		X						
Medical history including previous treatments	X								
Prior/concomitant medications	X	X	X	X	X	X	X	X	X
Physical examination	X							X	
Height	X								
Weight	X								
Vital signs (temperature, HR, BP & RR)[a]	X		X	X	X	X		X	X
12-lead ECG	X							X	
International Prostate Symptom Score (IPSS)[b]	X								
Digital rectal examination of the prostate	X								
Alcohol and tobacco screen	X								
Clinical laboratory[c]	X								
Serum testosterone[d]	X	X					X		
24-hour ABPM			X[e]					X[e]	

Table 3: Study Schedule of Activities – AVEED (Testosterone Undecanoate Injection) (Continued)

Procedures	Screening Phase Day -28 to -2	Baseline			Treatment Visits (± 3 days)		End-of-Study/Early Termination (± 3 days)		
		Day -1	Visit 1 Day 1	Return Visit Day 2	Study Visit Day 30	Study Visit Day 100	Day 106	EoS Visit Day 107	Return Visit Day 108
Confirm valid ABPM session[f]				X					X
Randomization[g]				X					
Study drug administration				X	X	X			
AEs/SAEs	X	X	X	X	X	X	X	X	X

[a] Temperature, heart rate (HR) and respiratory rate (RR) will be captured. BP will be measured, using a sphygmomanometer, at all office visits. Subjects will be seated on a chair with back rest, resting his flexed dominant arm on a flat surface so that his upper arm is at heart level. Subjects with BP > 140/90 mm Hg should be excluded from the study. Subjects receiving the AVEED injection will have vital signs taken before administration of the study drug. Site personnel will ensure that the same arm and cuff size will be used. Vital signs taken will include SBP and DBP, pulse rate, respiratory rate, and body temperature. The results, date, and time for all vital sign assessments will be recorded.

[b] International Prostate Symptom Score (IPSS) ≥ 19.

[c] Includes tests for hematology, biochemistry, serum prostate-specific antigen (PSA), and urine analysis.

[d] Two blood samples will be obtained for serum testosterone, at 10 AM (± 2 hours) on 2 separate occasions spaced at least 48 hours apart (± 1 hour).

[e] Onsite device activation.

[f] If a subject does not have a valid ABPM session (defined as ≥ 70% of expected measurements including 20 valid awake [0900-2100 h] and 7 valid sleep [0100-0600 h] measurements) at baseline or at the end of study visit the ABPM session can be re-done.

[g] A valid ABPM must be confirmed prior to a subject being randomized.

3.2. Eligibility Criteria for Subject Selection

3.2.1. Inclusion Criteria

In order to be eligible to participate in the study, at the Screening Visit and on Study Day 1, subjects must:

1. Be male and ≥ 18 years of age at the time of consent.
2. Have a diagnosis of primary hypogonadism (congenital or acquired) OR hypogonadotropic hypogonadism (congenital or acquired).
3. Have a total serum testosterone at Screening < 300 ng/dL based on 2 blood samples obtained at 10:00 am (± 2 hours) on 2 separate occasions at least 48 hours apart.
4. Be naïve to androgen replacement or washout of 12 weeks following intramuscular androgen injections; 4 weeks following topical or buccal or oral androgens. Washout should be completed by Study Day -2.
5. Have a screening BP at rest of less than 140 mm Hg for SBP and less than 90 mm Hg for DBP.
6. Be judged to be in good general health as determined by the principal investigator based upon the results of a medical history, physical examination, vital signs, laboratory profile and a 12-lead ECG performed at Screening.
7. Subjects enrolled in the TESTIM or FORTESTA treatment arms: Subjects agree to take necessary precautions (wear clothing over application sites, wash with soap and water, etc) to avoid skin-to-skin contact and potential transfer of TESTIM or FORTESTA to their female partner, children and/or others.
8. Subjects with reproductive potential enrolled in the TESTIM or FORTESTA treatment arms agrees to use effective contraception (abstinence, surgical sterilization [vasectomy], or condom with spermicide) with a female partner for the duration of the study and for 28 days after any active treatment period.
9. Be willing and able to cooperate with the requirements of the study.
10. Be adequately informed and understand the nature and risks of the study and be able to provide consent as outlined in Protocol Section 10.1.3.

3.2.2. Exclusion Criteria

A subject is ineligible for study participation if the subject:

1. Is from a vulnerable population, as defined by the US Code of Federal Regulations (CFR) Title 45, Part 46, Section 46.111(b) and other local and national regulations, including but not limited to, employees (temporary, part-time, full time, etc) or a family member of the research staff conducting the study, or of the sponsor, or of the contract research organization, or of the Institutional Review Board/Independent Ethics Committee (IRB/IEC).
2. Has a history of significant sensitivity or allergy to the study drugs, including androgens, or product excipients.

3. Has a history of or medical examination findings or concurrent diseases that might interfere with the conduct of the study, or endanger the subject's well-being, or any significant renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric conditions, cardiovascular disease/dysrhythmia or any other condition(s) that in the investigator's opinion might indicate the subject to be unsuitable for the study. If there is a history of such disease but the condition has been stable for more than 5 years and is judged by the investigator not to interfere with the subject's participation in the study, the subject may be included, with the documented approval of the Medical Monitor.
4. Is not on a stable medication regimen for at least 3 months for the treatment of a chronic condition such as hypertension, hyperlipidemia or diabetes mellitus.
5. Has had a cardiovascular and/or cerebrovascular event within 6 months prior to Study Day -2.
6. Needs a BP cuff size larger than 50 cm.
7. Works a night shift or performs heavy manual labor.
8. Has any known contraindication(s) to active study treatment including, but not limited to:
    a. Known or suspected carcinoma (or history of carcinoma) of the prostate, clinically significant symptoms of benign prostatic hyperplasia, and/or clinically significant symptoms of lower urinary obstruction and International Prostate Symptom Score (IPSS) ≥ 19. A clinically significant digital rectal examination of the prostate or clinically significant elevated serum prostate-specific antigen (PSA) levels (> 4.0 ng/mL).
    b. Known or suspected carcinoma (or history of carcinoma) of the breast and/or previous history of cancer (except basal cell carcinoma of the skin).
    c. Liver disease defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 × upper limit of normal (ULN) or bilirubin > 2 × ULN.
    d. Active deep vein thrombosis or thromboembolic disorder, or a documented history of these conditions.
    e. Atrial fibrillation.
    f. Untreated sleep apnea.
    g. Has known immune compromised status (not related to disease/condition under study), including but not limited to, individuals who have undergone organ transplantation or who are known to be positive for the human immunodeficiency virus.
9. Uses known inhibitors (eg, ketoconazole) or inducers (eg, dexamethasone, phenytoin, rifampin, carbamazepine) of cytochrome P450 3A (CYP3A) within 30 days prior to study drug administration and through the end of the study.
    a. Uses any of the above listed drugs within 5 half-lives of the last dose in the past 6 months prior to study drug administration.
    b. Has received any of the above listed drugs by injection within 30 days or 10 half-lives (whichever is longer) prior to study drug administration.

c. Uses neutraceuticals or homeopathic compounds which have a known effect on BP.

10. Has a history of drug or alcohol abuse within 6 months prior to study drug administration.
11. Has untreated moderate to severe depression.
12. Has any skin lesions/cuts/injury at the application site that prohibits topical application and/or intramuscular injection of study drug.
13. Has clinically significant changes in any medications (including dosages) or medical conditions in the 28 days prior to screening.
14. Has suspected reversible hypogonadism (eg, leuprolide injection).
15. Donated blood or blood products or experienced significant blood loss within 90 days prior to study drug administration.
16. Intends to conceive at any time during the study.
17. Donated bone marrow within 6 months prior to study drug administration.
18. Requires any unapproved concomitant medications as defined in the protocol that could not be discontinued or switched to an allowable alternative medication prior to the minimum allowable interval before baseline (Day 1).
19. Has participated in a previous investigational study or received treatment with an investigational product within 30 days (or 5 half-lives, whichever is longer) of screening.
20. Has a diagnosis of, is undergoing therapy for, or has received therapy for a hematologic malignancy in the 5 years prior to Screening.
21. Has a history of substance abuse or is taking any substance of abuse (Note: Subjects on a stable dose of any medications that have been prescribed by a healthcare practitioner for a properly documented medical condition are exempt).
22. Has evidence of abnormalities on physical examination, vital signs, ECG or clinical laboratory values, unless judged to be clinically insignificant by the investigator.
23. Has evidence of confirmed QT prolongation with QTc ≥ 450 ms.
24. Has any other condition that, in the investigator's opinion, might indicate the subject to be unsuitable for the study.

3.3. Randomization Criteria

At screening or Day 1, subjects with office BP readings of ≥ 140/90 will be considered screen failures; ie subjects with SBP ≥ 140 and/or DBP ≥ 90 will be considered screen failures. At Day 1, only subjects with office BP readings of < 140/90 will be eligible for randomization. A valid ABPM must be confirmed prior to subject being randomized.

3.4. Method of Assignment of Subjects to Treatment Groups

This is an open label study; however, eligible subjects will be randomly assigned to one of the following 3 treatment arms in a 1:1:1 ratio:

- Testosterone undecanoate injection (AVEED)

- Testosterone gel (FORTESTA)
- Testosterone gel (TESTIM)

Treatment assignment will be managed through an Interactive Response Technology (IRT) system.

3.5. Study Treatment

Subjects will be administered assigned study drug on Day 2 and will be instructed to continue applying/administering the study drug (not applicable for AVEED injection). The study treatment detail is explained in Table 4 below.

Table 4: Study Treatments

Product Name	Testosterone undecanoate injection (AVEED)[a]	Testosterone gel (FORTESTA)	Testosterone gel (TESTIM)
Type	Drug	Drug	Drug
Dose Formulation	Solution for Injection	Gel	Gel
Dose Amount and Frequency[b]	750 mg/3 mL Days 2, 30, and 100 (± 3 days)	40 mg once daily (in the morning)	50 mg once daily (in the morning)
Route of Administration	Intramuscular (IM) Injection Injection site: gluteus medius muscle	Topical Apply to upper inner thighs	Topical Apply to shoulders or upper arms

[a] AVEED will be used in accordance with the approved REMS.
[b] Detailed information on study drug administration will be available in a separate Pharmacy Manual.

3.6. Determination of Sample Size

The sample size is based on the primary efficacy endpoint of analyzing mean change from baseline to EoS in 24-hour average SBP to determine whether the study drugs have a clinically meaningful effect on ambulatory BP in hypogonadal men.

A sample size of 170 for each of the 3 treatment groups (AVEED, FORTESTA, and TESTIM) achieves 90% statistical power to exclude an upper bound of 3 mm Hg threshold SBP increase in 24-hour average systolic ambulatory blood pressure at EoS from baseline using 2-sided 95% confidence interval (CI) with paired *t* test. The standard deviation (SD) of 12 mm Hg is assumed.

It is assumed that 30% of enrolled subjects will be excluded from the Full Analysis Set (FAS) (ie, subjects who discontinue early from the study, non-valid ABPM measures at baseline or EoS, etc), therefore a sample size of 243 for each of the 3 treatment groups for a total of 729 is required.

3.7. International Prostate Symptoms Score (IPSS)

The International Prostate Symptom Score (IPSS) is a written screening tool used to screen for, rapidly diagnose, track the symptoms of, and suggest management of the symptoms of benign prostatic hyperplasia (BPH).(2)

IPSS is based on the answers to 7 questions concerning urinary symptoms and 1 question concerning quality of life. This assessment will be used for screening purposes only; this study will not use question 8 referring to perceived quality of life.

Table 5: IPSS Questionnaire

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
Incomplete Emptying Over the past month, how often have you had the feeling of not completely emptying your bladder after you finished urinating?	0	1	2	3	4	5	X
Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	X
Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	X
Urgency Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5	X
Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	X
Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	X
	None	**1 time**	**2 times**	**3 times**	**4 times**	**5 times or more**	**Your score**
Nocturia Over the past month, many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5	X
IPSS Total Symptom Score (sum of all the individual scores)							XX

The total symptom score shows the severity of the symptoms. The first 7 questions of the IPSS are identical to the question appearing on the American Urological Association Symptom Index, which currently categorizes symptom as follows:

[redacted]

Table 6: IPSS Total Symptom Score

Rating	Level of Severity	Description
1	Mild	Total symptom score ≤ 7
2	Moderate	Total symptom score range 8-19
3	Severe	Total symptom score range 20-35

3.8. Digital Rectal Examination of the Prostate

A digital rectal examination (DRE) is an important element of a clinical examination of the rectum and nearby organs, including the anal canal, prostate and bladder. It can detect conditions like an enlarged prostate (benign prostatic hyperplasia) and prostate cancer. This assessment will be recorded as normal and abnormal for screening purposes only.

3.9. Medical and Surgical History

A medical and surgical history of the subject will be taken during screening. Medical history will include relevant diagnoses and/or procedures/therapies with onset/resolutions dates.

Medical history will include a review of the following systems: general, dermatological, respiratory, cardiovascular, gastrointestinal, genitourinary, endocrine, musculoskeletal, hematological, neuropsychological, immune (allergies), and head, eyes, ears, nose, and throat. Historical and current medical conditions with onset/resolutions dates will be recorded.

3.10. Substance Use

History of tobacco and alcohol use will be taken during screening and the following information will be recorded:

- Type of substance (Alcohol/Tobacco)
- History of usage (Never/Currently/Former)
- Number of years the product was used (for current or former users)
- Stop date of using the product (for former users)

3.11. Prior and Concomitant Medications and Procedures

Any medications and non-drug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, etc) taken during the study or within 30 days prior to Screening visit will be recorded.

In addition, all prior treatments for the disease/condition under study administered in the previous 5 years will be recorded.

3.12. Prohibited Medications

Use of known inhibitors (eg, ketoconazole) or inducers (eg, dexamethasone, phenytoin, rifampin, and carbamazepine) of CYP3A are prohibited in this study. If any prohibited medication is taken during the study, all pertinent information will be recorded.

3.13. Efficacy Parameters

3.13.1. 24-Hour Ambulatory Blood Pressure Monitoring (ABPM)

ABPM will be performed using a 24-hour ambulatory blood pressure recorder machine. The device will be attached to the subject's arm at bicep level on Day 1. The machine will be set to measure BP every 30 minutes for the next 24 hours. The device will be returned to the study site by the subject on the following day (Day 2).

TESTIM and FORTESTA subjects will be instructed to visit the study center again on Day 114 to be fitted with the ABPM device to measure BP every 30 minutes for the next 24 hours, and on Day 115 to return the device.

AVEED subjects will be instructed to visit the study center again on Day 107 to be fitted with the ABPM device to measure BP every 30 minutes for the next 24 hours, and on Day 108 to return the device.

Baseline BP will be analyzed (systolic and diastolic means) for the overall 24-hour period, daytime (from waking up to bedtime) and nighttime (from retiring to bed until waking) for each subject.

3.14. Safety Parameters

3.14.1. Adverse Events

All adverse events (AE) will be recorded from the time informed consent is signed through the EoS visit or for 28 days after the last dose of the study treatment for those who terminate early. Conditions existing prior to screening will be recorded as part of subject's medical history.

3.14.1.1. Adverse Events (AEs)

An AE is any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result (eg, chemistry, ECG, X-ray, etc), or worsening of a pre-existing condition associated temporally with the use of the study medication whether or not considered related to the study medication. This would include AEs resulting from concurrent illness, reactions to concurrent medication use, or progression of disease states (excluding the disease under study). A condition present at baseline that worsens after initiation of study treatment will be captured as an AE; the onset date will be the date the event worsened.

3.14.1.2. Serious Adverse Events (SAEs)

Serious adverse event are those AEs that meet any of the following criteria:

- Results in death
- Life-threatening event
- Results in or prolongs an inpatient hospitalization
- Results in permanent or substantial disability
- Is a congenital anomaly or birth defect

- Any important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

3.14.2. Clinical Laboratory Determinations

Blood and urine samples will be collected at the Screening visit for testing the clinical laboratory parameters shown in Table 7 below. Testing includes serum PSA.

Table 7: Clinical Safety Laboratory Parameters

Hematology	Biochemistry	Urinalysis
Hemoglobin	Glucose	Glucose
Hematocrit	Sodium	Protein
Red blood cell	Potassium	Specific gravity
White blood cell (WBC)	Calcium	pH
Platelets	Chloride	Ketones
WBC Differential	Carbon dioxide (CO_2)	Bilirubin
	Inorganic phosphate	Urobilinogen
	Blood urea nitrogen	Nitrite
	Creatinine	Blood[a]
	Creatinine clearance (estimated)	Leukocytes[a]
	Aspartate transaminase (AST)	
	Alanine transaminase (ALT)	
	Gamma-glutamyl transferase (GGT)	
	Total bilirubin (TBL) (direct bilirubin reflex if elevated)	
	Albumin	
	Alkaline phosphatase (ALP)	
	Uric acid	

[a] Microscopic examination will be performed if blood or leukocytes are detected by dipstick.

Any clinically significant laboratory abnormality observed will be considered as an AE or SAE as appropriate.

3.14.3. Serum Testosterone Assessment

Blood samples of approximately 100 mL will be collected for analysis of serum testosterone from all subjects participating in the study during Screening (2 separate times), Baseline (Day -1), Treatment Follow-up visits, and EoS visit as mentioned in SoA table (see Table 2 and Table 3).

3.14.4. Height and Weight

Height will be collected at screening only. Weight will be obtained at the Screening visit only for AVEED, and at Screening, Baseline (Day 1), Treatment Follow-up visits, and EoS visit for TESTIM and FORTESTA treatment arms.

Any clinically significant abnormality in weight compared to the screening value will be considered as an AE or SAE as appropriate.

3.14.5. Vital Signs

Vital signs measurements (SBP, DBP, HR, RR, and body temperature) will be taken at Screening, Baseline (Day 1 and 2), Treatment Follow-up visits, and EoS (Day 114 and 115 for TESTIM and FORTESTA, Day 107 and 108 for AVEED) visit.

For subjects receiving the AVEED injection, vital signs will be taken before administration of the study drug.

For all subjects, vital signs will be obtained after the subject has been seated for 5 minutes (minimum), with feet flat on the floor and back supported.

Subjects with BP ≥ 140/90 mm Hg (SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg) at screening will be excluded from study participation.

Any clinically significant abnormality in vital signs observed will be considered as an AE or SAE as appropriate.

3.14.6. Electrocardiogram

A 12-lead ECG will be performed during the Screening and EoS (Day 114 for TESTIM and FORTESTA, Day 107 for AVEED) visits while the subject is in a supine position for at least 5 minutes before the recording is conducted.

If the ECG report shows QT prolongation with QTc ≥ 450 ms, the investigator will repeat the ECG within 1 hour. If the initial findings are confirmed, the investigator will exclude the subject from study participation.

ECGs will be assessed by the investigator and graded as:

- Normal
- Abnormal, not clinically significant
- Abnormal, clinically significant

Any clinically significant abnormality in ECG observed will be considered as an AE or SAE as appropriate.

3.14.7. Physical Examination

The complete physical examination (by body system) on each subject will be performed at the Screening and EoS (Day 114 for TESTIM and FORTESTA, Day 107 for AVEED) visits. Physical examination will include: evaluation of the head, eyes, ears, nose, throat, neck (including thyroid), cardiovascular system (including assessment of heart, peripheral pulses, presence or absence of edema), genitourinary system, lungs, abdomen (including liver and spleen, bowel sounds), lymph nodes, musculoskeletal system (including spine, joints, muscles), neurological system (including cranial nerves, reflexes, sensation, strength), skin, extremities, and other conditions of note.

The investigator will assess the physical examination findings as normal or abnormal. If physical examination findings meet the investigator's criteria for clinical significance, they will be reported as an AE or SAE as appropriate.

3.14.8. Study Treatment Compliance

Prior to beginning the administration of study treatment, subjects and/or their caregiver will be trained on dosing and mode of administration and must exhibit proper technique.

Study drug compliance during each study visit/any period for the FORTESTA and TESTIM treatment arms will be calculated via weight and/or count of containers to determine treatment compliance. Subjects using too much, or too little study drug should be re-educated on the proper use of study drug. Repeated noncompliance (less than 85% or greater than 100%) should be evaluated for the need to withdraw the subject.

4. STUDY PARAMETERS

4.1. Subject Disposition

A subject will be considered to have completed the study if the subject has completed the 2-day EoS visit.

Subjects who discontinue or are withdrawn from study treatment will be encouraged to complete the remaining study visits and evaluations and provide any additional follow-up information as required by the study, unless the subject specifically indicates that they will not participate in any further evaluations. The reason and date for study treatment discontinuation will be recorded in the electronic case report form (eCRF).

If a subject withdraws from the study, all EoS/ET procedures will attempt to be conducted as detailed in the SoA. The reason and date for early withdrawal will be recorded in the eCRF for subjects who do not complete the study. If, however, a subject withdraws consent, no additional procedures are required except the collection of AE information. This information will be recorded in the source documentation and the eCRF.

Subjects who discontinue from the study treatment or who have been lost to follow-up at any time after the first dose of the study drug will not be replaced.

The reason for screen failure will also be recorded in eCRF for subjects:

- who consent to participate in this study but are not subsequently randomized
- who do not meet all of the eligibility criteria prior to randomization

Subjects who do not meet all the eligibility criteria and are considered screen failures may be rescreened once.

4.2. Protocol Deviations

Potential deviations will be identified prior to database lock. Protocol deviations will be derived from the eCRF data, electronic vendor data, and will be obtained from the clinical monitoring reports. All deviations from these sources will be reconciled and duplicate deviations will be removed.

Possible protocol deviations include, but are not restricted to the following deviation types:

- Ineligible subject/study entry criteria not satisfied

- Informed consent not completed correctly
- Non-compliance of study treatment
- Prohibited medications/procedure
- Visit/procedure missing or out of window

The study team will approve all final protocol deviation assignments and classify them as either major or minor during ongoing protocol deviation review meetings held throughout the study and a final meeting prior to the database lock.

All study assessments conducted outside of the allowed windows outlined in the Schedule of Activities due to a COVID-19 interruption will be documented as a protocol deviation. COVID-19 will be recorded as the reason for these out-of-window assessments.

4.3. Demographic and Baseline Characteristics

Demographics and baseline characteristics include the following parameters:

- Age
- Age group (< 45 years, 45-64 years and ≥ 65 years)
- Height (at Screening)
- Weight (at Screening)
- Body Mass Index (BMI) in kg/m^2 (at Screening)
- Gender (Male)
- Race
- Race group (African Americans and Others)
- Ethnicity
- Report of tobacco and alcohol use
  - Alcohol use (Never, Current, and Former)
  - Tobacco use (Never, Current, and Former)
- IPSS (at Screening)
- Digital rectal examination of the prostate (at Screening)
- Serum prostate-specific antigen (at Screening)
- Hypertension Classification (subjects without hypertension, with hypertension untreated, and with hypertension treated)
- Diabetes status (Yes and No)

4.4. Prior and Concomitant Medications/Therapies

All medications will be coded using World Health Organization (WHO) Drug Dictionary, by active ingredient and WHO anatomical therapeutic chemical (ATC) classification of ingredients. The dictionary version to be used will be defined in the Data Management Plan (DMP).

A prior medication is defined as any medication taken within the 30 days prior to and stopped before the Screening visit.

A concomitant medication (or non-drug therapy) is any medication (or therapy) taken on or after the Screening visit through the EoS visit or taken prior to the Screening visit and continuing during the study.

A new antihypertensive medication is any antihypertensive medication taken on or after the Screening visit through the EoS visit and not taken prior to the Screening visit.

4.5. Efficacy Parameters

4.5.1. Valid ABPM Session

An ABPM session is defined as valid if there is ≥ 70% of expected measurements including at least 20 valid awake [0900-2100 h] and at least 7 valid sleep [0100-0600 h] measurements.

4.5.2. Primary Efficacy Parameters

4.5.2.1. Mean Change from Baseline in 24-hour Average Systolic Ambulatory Blood Pressure

24-hour average systolic ambulatory blood pressure is computed by averaging hourly systolic ambulatory blood pressures. The hourly systolic ambulatory blood pressure is the average of observed systolic ambulatory blood pressure measurement within an hour.

$$24 - \text{Hour Average SBP} = \frac{1}{24}\sum_{i=1}^{24} SBP_i\,;$$

where SBP_i is systolic ambulatory blood pressure at i^{th} hour.

Baseline: 24-hour average systolic ambulatory blood pressure at baseline visit will be baseline for the primary endpoint, observed systolic ambulatory blood pressure and hourly average systolic ambulatory blood pressure.

To measure the change in daytime, the hourly average systolic ambulatory blood pressure observed/measured during 0900 to 2100 hours will be baseline. To measure the change in nighttime, the hourly average systolic ambulatory blood pressure observed/measured during 0100 to 0600 hours will be baseline.

24-hour average systolic ambulatory blood pressure will be assessed at Baseline and EoS visits. The mean change from Baseline in 24-hour average systolic ambulatory blood pressure at the EoS visit will be analyzed.

4.5.3. Secondary Efficacy Parameters

4.5.3.1. Mean Change from Baseline in 24-hour Average and Time Windows of Interest in ABPM Parameters

The mean change from Baseline in 24-hour average, and at each time windows of interest or time point (ie, time windows, daytime [0900-2100 hours], and nighttime [0100-0600 hours]) will be analyzed for the following parameters:

- MAP
- SBP
- DBP
- PP
- HR

The maximum change from baseline during the 24-hour duration will also be analyzed for the above-mentioned ABPM parameters.

Computational formula for MAP and PP is defined in Table 12.

4.5.4. Change from Baseline Over Time in ABPM Parameters

There will be 2 readings (1 reading every 30 minutes) per hour for 24-hour recordings except for the first hour. For the first hour, there will be 3 readings (at 0, 30, and 60 minutes). The mean change from baseline over time (hourly average) will be analyzed by nominal clock time for the following parameters:

- MAP
- SBP
- DBP
- PP
- HR

4.5.5. Subjects with Antihypertensive Medication

Antihypertensive medications are the class of drugs that are used to treat hypertension (high blood pressure). The antihypertensive class of medications will be identified from the concomitant medication page of the eCRF and will be reviewed by the medical monitor; the dose of antihypertensive medication will be captured on the eCRF. The percent of subjects with new antihypertensive medications and percent of subjects with dose increases in antihypertensive medications will be evaluated.

4.5.5.1. Ambulatory Blood Pressure Thresholds

Blood pressure threshold values are presented in Table 8 below.

Table 8: Blood Pressure Thresholds

Parameter	Thresholds
SBP	≥ 160 mm Hg and/or ≥ 20 mm Hg increase from baseline
DBP	≥ 100 mm Hg and/or ≥ 15 mm Hg increase from baseline

4.6. Safety Parameters

4.6.1. Extent of Exposure to Study Treatment

The duration of study drug exposure will be summarized. In case of early withdrawal, the early withdrawal date will be used to calculate the exposure duration. Refer to Table 12 for duration of exposure formula.

4.6.2. Adverse Events

Adverse event verbatim terms as reported by the investigator will be mapped to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The dictionary version to be used will be defined in the DMP.

4.6.2.1. Treatment Emergent Adverse Events (TEAEs)

TEAEs are defined as any AEs that occur or worsen (increase in severity) on the same day or after the treatment initiation.

The following rules will apply in cases where the start date of an AE is known:

- If the AE onset date is prior to first application/administration of the study drug, then the AE will not be considered a TEAE.
- If the AE onset date or date of AE worsening is equal to or later than first application/administration of the study drug, then the AE will be considered a TEAE.

Refer to Section 6.5.1.1 to identify TEAE status when start date of an AE is unknown.

4.6.2.2. Intensity of Adverse Events

Intensity (or severity) of AEs will be graded as “Mild”, “Moderate” or “Severe”. For AEs with missing severity, the most severe assessment will be imputed for analyses, following worst case principle.

4.6.2.3. Relationship to Study Drug

Causal relationship of AEs to study drug will be classified by the investigator and will be reported as follows:

- Not related
- Unlikely related
- Possibly related
- Probably related

Related adverse events are AEs with the relationship described by the investigator as "Probably related" or "Possibly related". "Not related" or "Unlikely related" causality assessments are considered as negative causality.

Any missing relationship of an AE to study drug will be considered as related to study drug for the analyses, following worst case principle.

4.6.3. Vital Signs and Clinical Laboratories

4.6.3.1. Potentially Clinically Important Laboratory Values

Potentially Clinically Important (PCI) laboratory values are presented in Table 9 below.

Table 9: Potentially Clinically Important Laboratory Criteria

Parameter	PCI Low: Less than or equal to	PCI High: Greater than or equal to
Hemoglobin (g/L)	100	190
Hematocrit (%)	30	60
Platelets (10^9/L)	100	650
ALT (U/L)		3×ULN
AST (U/L)		3×ULN
Creatinine (µmol/L)		300
BUN (mmol/L)		12

BUN=Blood urea nitrogen

4.6.3.2. Potentially Clinically Important Vital Sign Values

Vital sign values are PCI if they meet both the observed value criteria and the change from baseline criteria. The PCI vital sign values are presented in Table 10 below.

Table 10: Potentially Clinically Important Vital Sign Criteria

Parameter	PCI Low	PCI High
Systolic Blood Pressure	≤ 90 mm Hg and decrease ≥ 20 mm Hg from baseline	≥ 180 mm Hg and increase ≥ 20 mm Hg from baseline
Diastolic Blood Pressure	≤ 50 mm Hg and decrease ≥ 15 mm Hg from baseline	≥ 105 mm Hg and increase ≥ 15 mm Hg from baseline
Heart Rate	≤ 50 bpm and decrease ≥ 15 bpm from baseline	≥ 120 bpm and increase ≥ 15 bpm from baseline
Respiratory Rate	≤ 8 brpm and decrease ≥ 7 brpm from baseline	≥ 25 brpm and increase ≥ 7 brpm from baseline
Temperature		≥38.3°C and increase ≥1.1°C from baseline

bpm=Beats per minute, brpm=Breaths per minute

5. ANALYSIS POPULATIONS

The study will use the following analysis populations for data summaries.

Table 11: Analysis Populations

Population	Definition	Displays
Safety Population	The Safety Population will include all subjects who have at least 1 dose/injection of study medication.	All demographic, baseline characteristics and safety parameters will be summarized based on this population.
Intent-to-Treat (ITT) Population	The ITT Population will include all randomized subjects who have at least 1 dose/injection of study medication.	Sensitivity analyses on primary and secondary endpoints to assess the impact of missing ABPM data at EoS will be based on this population.
FAS	The FAS will include all ITT subjects with valid baseline and EoS ABPM assessments.	All primary and secondary efficacy analysis will be based on this population.
ABPM Population	The ABPM Population will include all subjects in FAS with at least 85% compliance to treatment during the study.	All primary and secondary efficacy parameters as a part of sensitivity analysis will be analyzed based on this population.

6. STATISTICAL METHODS

6.1. General Methodology

All statistical tests, summary tables and data listings will be prepared using SAS version 9.4.

All statistical tests of efficacy parameters will be 2-sided with a significance level of α=0.05, unless specified otherwise. Statistical tests will be supported by presenting estimates and 95% CI for each treatment group. These estimates and CIs will be based on the linear regression model.

Continuous data will be summarized using descriptive statistics (number of subjects [N], mean, SD, median, minimum, and maximum). Discrete data will be summarized using frequency counts and percentages. The denominator will be based on the number of subjects in the appropriate population.

For the purpose of display, the summary results will be rounded as follows:

- Minimum and maximum: same number of decimal places as the raw data.
- Mean and median: 1 more decimal place than the raw data.
- SD: 2 more decimal places than the raw data.
- Percentages will be displayed with 1 decimal place precision. A zero count will be left blank.
- The standard form of a percentage change variable is 1 decimal place.

For categorical variables with missing values, a category documenting the frequency of missing values will be displayed in the summary tables.

Summary tables, subject listings, graphs and any supportive SAS output will include footnotes that will indicate:

- date of data extraction
- date and time of output generation
- SAS program name, including the path, that generated the output

When calculating percentages, the denominator will be based on the number of subjects with non-missing values. If the denominator is expected to change over time, then the denominator used to calculate the percentage will be based on the number of subjects with non-missing values at each visit. Any subject removed from an analysis will be noted at the bottom of the table along with the reason the subject was removed.

Empty summary tables will be presented with a note stating that "No Subjects Met Criteria."

Subject listings of all data from the eCRFs as well as any derived variables will be presented.

6.2. Adjustments for Covariates

The baseline value of the efficacy parameter and study center (or pooled centers, if applicable) will be used as a covariate in the statistical model.

6.3. Examination of Subgroups

Exploratory subgroup analyses will be performed on the primary, secondary, and outlier analyses. The subgroups are:

- Hypertension classification (subjects without hypertension, with hypertension untreated, with hypertension treated)
- Race (African Americans and Other)
- Age group (< 45 years, 45-64 years and ≥ 65 years)
- Diabetes status (Yes and No)
- Tobacco use status (Never, Current and Former)

6.4. Derived Variables

Table 12 defines the derived variables for study parameters.

Table 12: Derived Variables and Definition

Variable	Definition
Age Group	< 45 Years 45-64 Years ≥ 65 Years
Height (cm)	If height is recorded in inches, then height is equal to the recorded value multiplied by 2.54 and then rounded to 1 decimal place.
Weight (kg)	If weight is recorded in pounds, then weight is equal to the recorded value multiplied by 0.454 and then rounded to 1 decimal place.
Body Mass Index (BMI)	BMI will be computed using height and body weight measured at Screening as BMI (kg/m^2) = Weight (kg) / Height $(m)^2$
Race Group	African Americans Other
Hypertension Classification	Subjects without Hypertension Subjects with Hypertension Untreated Subjects with Hypertension Treated
Baseline Diabetes Status	Yes No
Tobacco Use Status	Never Current Former
Relative Day 1	The designated Day 1 when eligible subject comes to study centres for ABPM will be considered as relative Day 1
Study Day (for assessment on or after Day 1)	Study Day will be computed as, Date of Assessment – Date of Day 1 + 1
Study Day (for assessment before Day 1)	Study Day will be computed as, Date of Assessment – Date of Day 1
Baseline	Baseline is defined as the last non-missing measurement/assessment prior to the first dose of study drug. Baseline for ambulatory parameters (SBP, DBP, PP, MAP and HR) is derived in Section 4.5.2.1.
Change from Baseline	Change from baseline will be derived as, post-baseline visit/time point value – the baseline value.
Last Date in Study	The date of Day 115 if the TESTIM and FORTESTA subjects complete the study The date of Day 108 if the AVEED subjects complete the study. The date of ET visit if the subject is terminated early from study at a non-scheduled visit. The date of the latest scheduled visit if the subject is terminated early from study at a scheduled visit or lost to follow-up.
PP	PP is computed as (SBP-DBP)
MAP	MAP is computed as [SBP + 2 (DBP)]/3
Duration of Exposure	Date of last dose of study medication – Date of first dose of study medication + 1
Duration of AE	AE end date – AE start date + 1
AE Onset Day (for AE onset date on or after date of first applying/ administering the study drug)	AE start date - Date of first applying/administering the study drug + 1
AE Onset Day (for AE onset date before date of first applying/ administering the study drug)	AE start date - Date of first applying/administering the study drug

6.5. Handling of Missing Data

The subjects having missing value at baseline for age, race, hypertension status, and diabetes status will be excluded from corresponding subgroup analyses (see Section 7.6.5 for subgroup analyses). Missing value for these variables will not be imputed.

6.5.1. Missing data handling for Primary and Secondary Analyses

24-hour average ABPM parameters at EoS: ABPM post baseline is performed at EoS; the readings are taken every 30 minutes for 24 hours. Hourly average and 24-hour average ABPM at EoS are derived from these 49 readings.

The subjects can have missing data for 24-hour average ABPM at EoS in following two cases:

(i) Subject discontinued the study without any ABPM assessment done.

(ii) Subject does not have valid ABPM session to compute 24-hour average value

Primary and secondary efficacy analyses will be on FAS. Only subjects with valid ABPM measurements at baseline and EoS will be analyzed.

Sensitivity analyses mentioned below will be done to assess impact of missing 24-hour ABPM measurement at EoS. No sensitivity analyses described in Section 7.6.4.2 will be performed if only less than 10% subjects in each treatment group has missing 24-hour average ABPM measurement at EoS.

Multiple Imputation: Missing change from baseline 24-hour average ABPM measurement at EoS will be imputed using Multiple Imputation (MI).

Mixed Model Repeated Measure: Mixed Model Repeated Measures (MMRM) analysis will be conducted using hourly average based on observed ABPM measurements.

Refer Section 7.6.4 for details regarding sensitivity analyses.

6.5.2. Missing data handling for Safety Data

There will be no imputation of missing values for safety data, however missing relationship between AE and study drug will be considered as related to study drug following worst case principle. Missing severity of an AE will be summarized as a severe AE.

6.5.3. Imputation of Partial Dates

6.5.3.1. TEAE Status for Completely Unknown Start Date

The following rules will apply in cases where start date of an AE is completely unknown:

- If the AE onset date is unknown and the end date is after first application/ administration of the study drug on Day 1 or ongoing, then the AE will be considered a TEAE.
- If the AE onset date is unknown and the end date is before first application/ administration of the study drug on Day 1, then the AE will not be considered a TEAE.

- If both the start and end dates are unknown (or end date is ongoing), then the AE will be considered a TEAE, following the worst-case principle.

If the AE onset date is partly present and month/year is prior to the first application/ administration of the study drug date, then the AE will not be considered a TEAE.

6.5.3.2. Concomitant Status of Medication/Non-drug Therapy for Completely Unknown Start Date

The following rules will apply in cases where start date of medication/therapy is completely unknown:

- If the onset date is unknown or partially present and the end date is after the date of screening but before the EoS visit or medication/therapy is ongoing, then the medication/therapy will be considered as concomitant.
- If the onset date is unknown or partially present and the end date is before the date of screening, then the medication/therapy will not be considered as concomitant.
- If both the start and end dates are unknown, then the medication/therapy will be considered as concomitant. This approach is considered to be the most conservative following the worst-case principle.

If the end date is partly present and month/year is prior to the date of screening, then the medication/therapy will not be considered as concomitant. If the onset date or end date is partly present and month/year for either of them is after to the date of screening or medication/therapy is ongoing, then the medication/therapy will be considered as concomitant.

6.6. Pooling of Centers

In the event that a site has fewer than 5 subjects, site will be considered to have an insufficient number of subjects and will be considered eligible for pooling.

Any sites with fewer than 5 subjects will be ordered numerically in ascending order, based on the investigator number. The median number of subjects in the sites where the number of subjects ≥ 5 subjects will be estimated. Sites with 4 or fewer subjects will be sequentially pooled in ascending order of site number until the resulting pseudo-site has at least as many subjects as the median size of the other sites. A new pseudo-site to account for additional low-enrolling sites will be started upon achieving the median number of subjects. The process will be repeated until there are no sites with subjects less than 5.

The list of pooled study centers will be finalized prior to database lock.

6.7. Interim Analyses

No interim analysis is planned in this study.

7. STATISTICAL ANALYSES

7.1. Subject Disposition

The number of subjects included in each study population will be summarized by treatment group. Subjects excluded from the analysis populations will be listed.

The frequency counts and percentages of subjects screened, completed, and discontinued from the study treatment and/or withdrawn from the study, as well as the reason for withdrawal from study and reason for discontinuation of study drug will be summarized by treatment group.

A listing of disposition data will be provided. Screen failure reasons will also be listed. In addition, listing for inclusion/exclusion criteria will also be presented.

7.2. Protocol Deviations

Protocol deviations will be divided into categories and severity (major/minor) and summarized by category, severity (major/minor), and treatment group. A listing of all protocol deviations will be presented.

7.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group for the Safety Population.

Age, height (at baseline), body weight (at baseline) and BMI in kg/m^2 will be summarized as continuous variables using descriptive statistics.

Gender, race, ethnicity, age group, race group, hypertension classification, and diabetes status will be summarized as categorical variables using frequency counts and percentages.

Refer to Table 12 for descriptions of age categories, race group, hypertension classification and diabetes status.

The following baseline characteristics will be summarized as categorical variables using frequency counts and percentages:

- International Prostate Symptom Score (IPSS) (at Screening)
- Digital rectal examination of the prostate (at Screening)
- Report of tobacco and alcohol use
  - Alcohol use (Never, Current, and Former)
  - Tobacco use (Never, Current, and Former)

Serum PSA will be summarized as continuous variables using descriptive statistics.

The demographic and baseline characteristics will also be summarized using ITT, FAS, and ABPM Population only if these populations are not identical to Safety Population.

All demographic and baseline characteristics will be presented in a subject listing. In addition, all subgroup classifications (refer to Section 6.3) will be presented in a subject listing.

7.4. Medical and Surgical History

Medical history will be coded using the MedDRA dictionary. The version to be used will be defined in the DMP. Medical and surgical history data will not be summarized; however, a subject listing will be provided.

7.5. Prior, Concomitant Medications and Procedures

Prior and concomitant medication use will be summarized by treatment group using frequency counts and percentages for subjects in the Safety Population, by active ingredient within each ATC, with ATC and active ingredients ordered alphabetically. Multiple use of the same medication by a subject will be counted only once.

Listings of prior and concomitant medications and therapies/procedures will be provided for all subjects. Similarly, a separate listing of prior treatments for the condition will be provided.

A subject listing of prior treatments for the disease/condition under study administered in the previous 5 years will be provided.

7.6. Efficacy Analyses

Efficacy parameters will be summarized and analyzed by treatment group using the FAS.

7.6.1. Primary Analysis

7.6.1.1. Mean Change from Baseline in 24-hour Average Systolic Ambulatory Blood Pressure

The primary endpoint, the mean change from baseline to EoS in 24-hour average systolic ambulatory blood pressure, for each treatment group will be analyzed using an analysis of covariance (ANCOVA) model with treatment and study center (or pooled centers, if applicable) as fixed effect, and baseline 24-hour average systolic ambulatory blood pressure as covariate.

The least square mean and the corresponding 2-sided 95% CI for change from baseline in SBP will be provided for each treatment group. If the upper limit of the 2-sided 95% CI of mean change in SBP falls below 3.0 mm Hg, it will be concluded that the tested treatment does not have statistical significance in increasing of 24-hour average systolic ambulatory blood pressure.

The mean change from baseline to EoS in daytime average (0900–2100 hours) and nighttime average (0100–0600 hours) SBP for each treatment group will be analyzed similar to the primary efficacy endpoint.

A forest plot will be generated for least square mean and corresponding 2-sided 95% CI for change from baseline in SBP at EoS for 24-hour average, daytime average (0900–2100 hours), and nighttime average (0100–0600 hours) for systolic ambulatory blood pressure for each treatment group.

The descriptive statistics for observed and change from baseline for each time point, 24-hour average, daytime average (0900–2100 hours), and nighttime average (0100–0600 hours) systolic ambulatory blood pressure for each treatment group will be provided. The maximum change from baseline during 24-hour duration will also be summarized.

The mean of hourly average systolic ambulatory blood pressure at baseline and EoS along with corresponding SD will be graphically presented for each treatment group. The cumulative distribution function plots will also be plotted for the means of the daytime (0900–2100 hours), nighttime (0100–0600 hours), and 24-hour systolic ambulatory blood pressure for each treatment group at baseline and EoS.

7.6.2. Secondary Analysis

7.6.2.1. Mean Change from Baseline in 24-hour Average and Time Windows of Interest in ABPM Parameters

The mean change from baseline to EoS in 24-hour average ABPM parameters, ie, MAP, DBP, PP, and HR for each treatment group will be analyzed similar to the primary efficacy endpoint.

The mean change from baseline to EoS in daytime average (0900–2100 hours) and nighttime average (0100–0600 hours) DBP and MAP for each treatment group will be analyzed similar to the primary efficacy endpoint.

The descriptive statistics for observed and change from baseline for each time point, 24-hour average, daytime average (0900–2100 hours), and nighttime average (0100–0600 hours) for MAP, DBP, PP, and HR for each treatment group will be provided. The maximum change from baseline during 24-hour duration will also be summarized.

Forest plots will be generated for least square mean estimate of change from baseline and corresponding 95% CI at EoS for 24-hour average, daytime average (0900–2100 hours), nighttime average (0100–0600 hours) for DBP and MAP for each treatment group.

The mean of hourly average diastolic ambulatory blood pressure at baseline and EoS along with corresponding SD will be graphically presented for each treatment group. Cumulative distribution function plots will also be plotted for the means at baseline and EoS and mean changes at EoS of the daytime (0900–2100 hours), nighttime (0100–0600 hours), and 24-hour DBP for each treatment group.

7.6.2.2. Change from Baseline Over Time in ABPM Parameters

The observed and mean change from baseline over time (hourly average) for MAP, SBP, DBP, PP, and HR will be summarized by nominal clock time and timing after dosing using descriptive statistics for each treatment group.

The mean of hourly average for MAP, PP, and HR at baseline and EoS along with corresponding SD will be graphically presented for each treatment group.

7.6.2.3. Subjects with Antihypertensive Medication

The frequency counts and percentage of subjects with new antihypertensive medications and with dose increases in antihypertensive medications will be summarized for each treatment groups.

A subject listing for antihypertensive medications will be provided.

7.6.3. Outlier Analysis

In addition to the above analyses, an outlier analysis will be performed. This analysis will depict the frequency counts and percentages of number of subjects along with number of outlier observations in each treatment group who meet the following BP threshold criteria:

- ≥ 160 mm Hg SBP at EoS
- ≥ 100 mm Hg DBP at EoS
- ≥ 20 mm Hg increase from baseline SBP at EoS
- ≥ 15 mm Hg increase from baseline DBP at EoS

A subject listing for above listed outliers will be provided.

7.6.4. Sensitivity Analysis

7.6.4.1. Sensitivity Analysis on ABPM Population

In order to access the impact of treatment compliance primary and secondary analyses will be performed on ABPM Population using the same method as described in the Section 7.6.1.1.

7.6.4.2. Sensitivity Analysis on ITT Population

The following analyses will be performed on ITT Population to determine the robustness of the results and to assess the impact of the missing data.

7.6.4.2.1. Sensitivity Analysis for Association

Sensitivity analysis to assess the association between data missingness at EoS and baseline ABPM measurements, and data missingness at EoS and baseline characteristics will be performed for each treatment.

The subjects are classified into two groups based on 24-hour average ABPM measurement at EoS i.e. “observed” or “missing”. The proportion of subjects by age group (< 45 years, 45-64 years and ≥ 65 years), by race group (African Americans, and other), by hypertension category (no hypertension, hypertensive but on treatment, and hypertensive but not treated), and by diabetes status (Yes/No) will be summarized for observed and missing groups and Chi-square test will be used to determine statistical significance of the difference in proportions. The difference in mean age and baseline 24-hour average ABPM measurement for observed and missing groups will be analyzed using two sample t-test.

7.6.4.2.2. Sensitivity Analysis to Assess Impact of Missingness

Multiple Imputation Method

Missing change from baseline 24-hour average ABPM measurement at EoS will be imputed using model-based MI. The model-based MI process requires the data to have a monotone missing pattern. The imputation model for change from baseline for 24-hour average ABPM measurement at EoS will include treatment group and site/pooled sites, and covariate of baseline ABPM.

The model-based MI process will involve 4 principal tasks:

- Calculate the number of missing EoS values to be imputed (nmiss).
- Missing values will be filled in '10 x nmiss' times to generate '10 x nmiss' complete data sets.
- Perform the primary (refer Section 7.6.1) and secondary (refer Section 7.6.2 analyses on imputed data.
- Results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

The least square mean and associated 95% CI and standard error will be presented for each treatment group.

MMRM Method

The MMRM model will use all available hourly data at baseline and EoS.

The hourly average ABPM measurements will be analyzed using a MMRM model. The model will include treatment group and site/pooled sites as fixed effects, and treatment-by-visit-by-timepoint as interaction effect. The model will use timepoint as repeated component in the model.

An unstructured (UN) covariance structure will be applied for the MMRM. In the event the UN covariance matrix results in non-convergence of the model, then the auto-regressive [i.e. AR (1)] covariance structures will be used. Estimate statement in PROC MIXED (SAS®) will be constructed to estimate change from baseline at EoS for each treatment.

The least square mean for change from baseline and associated 95% CI, and standard error will be presented for each treatment group.

7.6.5. Subgroup Analyses

The primary, secondary, and outlier analyses will be repeated for the following subgroups:

- Baseline hypertension status (subjects without hypertension, with hypertension untreated, and with hypertension treated)
- Race Group (African Americans and Other)
- Age group (< 45 years, 45-64 years and ≥ 65 years)
- Diabetes status (Yes and No)
- Tobacco use status (Never, Current and Former)

The analysis will be based on the same methods described for the primary efficacy endpoint in Section 7.6.1.1.

7.7. Safety Analyses

Safety data will be summarized by treatment group using the Safety Population.

7.7.1. Study Drug Exposure

The duration of study drug exposure will be summarized descriptively for each treatment group.

A subject listing of overall exposure will be provided.

7.7.2. Adverse Events

All AE summary tables will include only TEAEs, unless otherwise specified.

AEs will be summarized by SOC and PT. A subject will only be counted once per SOC and PT.

For AEs by severity grade (mild, moderate, severe), if a subject has multiple events occurring in the same SOC or same PT, then the event with the maximum intensity (ie, severe) will be counted.

For AEs by relationship to study drug, if a subject has multiple events occurring in the same SOC or same PT, the event with the highest association (ie, related) to study drug will be summarized.

AEs will be presented in decreasing order of the incidences at SOC level and within each SOC, in decreasing order of the incidences at the PT level.

An overall summary of AEs and AEs related to study drug will be presented and will include:

- Total number of TEAEs reported
- Total number of TEAEs reported by severity
- Subjects with any TEAE
- Subjects with any serious TEAE
- Subjects with any severe TEAE
- Subjects with no severe TEAEs, but at least 1 moderate TEAE
- Subjects with no severe TEAEs, but at least 1 mild TEAE
- Subjects with any TEAEs leading to drug interruption/withdrawn
- Subjects with any TEAEs leading to study discontinuation
- Subjects with any TEAEs resulting in death

The following summary tables will be presented by SOC and PT:

- All TEAEs
- TEAEs by severity
- TEAEs by relationship to study drug
- All study drug related TEAEs
- Study drug related TEAEs by severity
- Serious TEAEs
- Serious study drug related TEAEs

- TEAEs leading to drug interruption/withdrawn
- Study drug related TEAEs leading to drug interruption/withdrawn
- TEAEs leading to study discontinuation
- Study drug related TEAE leading to study discontinuation
- TEAEs resulting in death
- Study drug related TEAEs resulting in death

Serious and most common non-serious TEAEs by order of frequency (most frequent, 2nd most frequent, and 3rd most frequent) will be summarized by PT. Serious and most common non-serious study drug related TEAEs by order of frequency (most frequent, 2nd most frequent, and 3rd most frequent) will be summarized by PT. Most common non-serious AEs are those that at least 5% of the subjects reported at least once (using PT).

The following listings will be presented by subject:

- All AEs
- Serious AEs
- AEs resulting in drug interruption/withdrawn
- AEs resulting in study discontinuation
- AEs resulting in death

Refer to Table 12 for computation of duration of AEs.

7.7.3. Clinical Laboratory

Actual value and change from baseline will be summarized by hematology and biochemistry laboratory parameters and study visit. In addition, a shift table will be provided for them between baseline and ET/EoS visit.

The PCI laboratory values will be summarized by frequency counts and percentages. Refer to Table 10 for PCI criteria.

A subject listing will be presented for all laboratory parameters (hematology, biochemistry and urinalysis).

7.7.4. Vital Signs

Vital signs (SBP, DBP, HR, RR, body temperature, and body weight) will be summarized for each treatment group using descriptive statistics for observed and change from baseline values for all assessment visits. A shift table will be provided for them between baseline and ET/EoS visit.

The PCI vital signs values will be summarized by frequency counts and percentages. Refer to Table 10 for PCI criteria.

A subject listing will be presented for vital signs results.

7.7.5. 12-Lead ECG

The investigator interpretation of ECG results (normal, abnormal not clinically significant or abnormal clinically significant) will be summarized using frequency counts and percentages at baseline and EoS visits by treatment group.

A subject listing will be presented for ECG results.

7.7.6. Physical Examination

A subject listing will be presented for the physical examination (by body system) Screening and EoS results.

7.8. Other Analyses

7.8.1. Serum Laboratory Testing

Serum testosterone and metabolites levels will be summarized using descriptive statistics for all assessment visits for each treatment group using the Safety Population.

In addition, for TESTIM and FORTESTA subjects, frequency counts and percentages will be presented for subjects with the same dose throughout the trial, doses titrated up and doses titrated down for all assessment visits using the Safety Population.

A subject listing will be presented for serum testosterone and metabolites levels/laboratory results.

8. CHANGE FROM PROTOCOL

This SAP is prepared based on the study protocol, Original version dated November 17, 2019 Amendment 1 dated March 19, 2020, and Amendment 2 dated September 15, 2020.(1)

Table 13 lists any significant changes in the SAP from what is proposed in the protocol.

Table 13: Changes from Protocol

Text in Protocol	Text in SAP	Justification
Section 9.2: All primary and secondary efficacy analysis will be based on the ABPM Population.	**Section 5:** All primary and secondary efficacy analyses will be based on FAS. The primary and secondary efficacy parameters as a part of sensitivity analysis will be based on ABPM Population. Additionally, sensitivity analyses to assess the impact of missing ABPM data at EoS will be based on ITT population.	Add FAS and ITT populations, in addition to ABPM population. FAS will be the primary population for primary and secondary analyses. ITT and ABPM populations will be used for sensitivity analyses.

9. REVISION HISTORY

SAP Module 2 is added.

10. REFERENCES

1. An open-label, randomized, parallel-group, three treatment arm, multicenter study on hypogonadal males to evaluate the effect on 24-hour ambulatory blood pressure after 16-week continuous treatment with marketed testosterone products [Clinical Study Protocol EN3000-101, Amendment 2]. Endo Pharmaceuticals Inc.; September 15, 2020.
2. International Prostate Symptom Score (IPSS) - The Management of Lower Urinary Tract Symptoms in Men, 1992, International – Prostate Symptom Score© (I-PSS©) Michael J. Barry.