Endo Pharmaceuticals Inc.
1400 Atwater Drive
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PROTOCOL NUMBER: EN3000-101

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

IND 072297: EN3331 (AVEED®)
IND 076634: EN3350 (FORTESTA®)
IND 061307*: EN3834 (TESTIM®)

*Auxilium Pharmaceuticals, LLC (Auxilium; formerly Auxilium Pharmaceuticals, Inc.) was acquired by Endo International plc in January 2015. The sponsor of the application remains Auxilium; however, Endo Pharmaceuticals Inc. (Endo) is authorized to act and to communicate on behalf of Auxilium. The sponsor is responsible for the conduct of the study, analysis of the data, and preparation of the clinical study report.

Original Protocol: 17 November 2019
Protocol Amendment 1: 19 March 2020
Protocol Amendment 2: 15 September 2020
Protocol Amendment 3: 28 September 2021
Protocol Amendment 4: 28 February 2022

[redacted]

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Overall Rationale for the Amendment 4

The inclusion of reserve samples was removed from Section 8.1.1 and the sample size was decreased.

Minor changes throughout the protocol amendment included wording changes for clarity, correction of minor typographical errors and revision of abbreviations.

Major changes are listed below.

Section No. and Name	Description of Change	Brief Rationale
Section 1.2 Schedule of Activities, Table 1 - Testim and Fortesta Section 4.1.5.1 Testim and Fortesta Treatment Arm	Added visit windows of ±3 days to the Days 113 and EOS Day 114 visits.	Removed visit window from the EOS/ET heading and included the windows with visits as required.
Section 1.2 Schedule of Activities, Table 2 - Aveed Section 4.1.5.2 Aveed Treatment Arm	Added visit windows of ±3 days to the Days 106 and EOS Days 107 visits.	Removed visit window from the EOS/ET heading and included the windows with visits as applicable.
Section 1.2 Schedule of Activities, Table 1Testim and Fortesta	Inserted footnote ‘c’ indicating that testosterone values collected at Screening will be used for evaluating study inclusion.	To provide clarification that Day -1 testosterone laboratory values are not available or needed for Day 1 eligiblity assessments.
Section 1.2 Schedule of Acitivities, Table 2 Aveed	Inserted footnote ‘d’ indicating that testosterone values collected at Screening will be used for evaluating study inclusion.	To provide clarification that Day -1 testosterone laboratory values are not available or needed for Day 1 eligiblity assessments.
Section 4.1 Overall design and Synopsis	Added that 618 subjects will be enrolled in 3 treatment groups.	Consistency with modified sample size.
Section 5.2 Subject Exclusion Criterion, #3	Deleted > 5 years when defining stable disease. Removed reference to oncologic.	Deletion of > 5 years applied to clarify that stable disease is at the discretion of the investigator rather than for > 5 years. Removed oncologic since this is detailed in exclusion criterion 8b.
Section 5.2 Subject Exclusion Criterion, #8.b	Clarified the exclusion criteria to include cancer or a previous history of cancer or relapse of cancer within the previous 5 years.	Allows PI to determine appropriateness of subject for inclusion in study. The Prescribing Information indicates that carcinoma of the prostate and breast are contraindicated, not testicular cancer and other types of malignancies.
Section 5.2 Subject Exclusion Criterion, #23 Section 8.1.6 Electrocardiogram	Revised QTc to QTcF	Updated QTc to QTcF throughout the protocol for consistency with the method of calculation described in Section 7.1

Section No. and Name	Description of Change	Brief Rationale
Section 8.1.1 Serum Testosterone Assessment	Removed the paragraph regarding blood reserve levels.	Reserve samples will no longer be collected. Clarified that testosterone samples collected at Screening will be used for study inclusion. Testosterone samples collected at Day -1 will be used as a baseline for the study.
Section 9.1 Sample Size Determination	Sample size was recalculated from 243 per group (total 729) to 206 per group (total 618).	Change in sample size was derived from a study or oral testosterone decanoate (White 2021), demonstrating an increase in systolic blood pressure with standard deviation of 11.
Section 10.1.8, Source Documentation	Modified retention of source documentation from 2 years to 3 years.	Align with Endo's internal policies.
Section 12, References	Added reference to White 2021.	Used to support the change in standard deviation from 12 to 11 referenced in Section 9.1

Overall Rationale for the Amendment 3

The inclusion of testosterone metabolites was removed from the description of laboratory testing. The projected date for trial completion was revised to December 2022 based on an anticipated enrollment of 50 subjects per month at 25 sites.

Minor changes throughout the protocol amendment included wording changes for clarity, correction of minor typographical errors and revision of abbreviations.

Major changes are listed below.

Section No. and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Study Period	Date of trial completion revised to December 2022	Reflects the delay in trial enrollment due to the Covid-19 pandemic.
Section 7.2 Subject Discontinuation/Withdrawal from the Study	Removed the phrase 'except the collection of AE information' from the last paragraph.	Removed to reflect that once a subject withdraws consent, no further procedures can be done.
Section 9.3.3 Serum Laboratory Testing	The mention of testosterone metabolites was removed laboratory testing.	Removed the mention of testosterone metabolites to reflect that metabolites were not planned to be analyzed as total testosterone level is being used to assess safety, study drug compliance and titration.

Overall Rationale for the Amendment 2

Rescreening language has been added to allow the assessments performed in the initial screen to be used if no more than 30 days have passed since the assessments were performed and the assessments are considered valid. The urine drug screen was removed as subjects were having positive urine drug screen results from the components of prescribed medications, (ie, Adderall for attention deficit disorder [ADD] showed positive for amphetamine). Exclusion criterion #21 was modified for clarity.

Major changes are listed below.

Section No. and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Date of first subject enrolled updated to June.	
Section 1.2 Schedule of Activities, Table 1 footnote 'c'	The following text was added: 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.	To clarify how vital signs are to be taken.
Section 1.2 Schedule of Activities, Table 2 footnote 'a'	The following text was added: 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.	To clarify when vital signs are to be taken in relation to the study drug.
Section 1.2 Schedule of Activities, Table 1 and Table 2	Urine Drug Screen was removed from the SOA.	Removed because some subjects had positive urine drug screen results from the components of prescribed medications.
Section 1.2 Schedule of Activities, Table 2	Serum testosterone footnote 'd' was moved from the Procedures column to the Screening Phase column.	
Section 1.2 Schedule of Activities, Table 2	The first 24-hour ABPM was moved from the Return Visit – Day 2 column to the Visit 1 Day 1 column.	The screening period was expanded from 14 days to 28 days to accommodate the time needed to obtain the results of the clinical laboratory testing performed.
Section 1.2 Schedule of Activities, Table 1 and Table 2	The heading for the Screening Phase was revised from 'Day -14 to -2" to "Day -28 to -2."	
Section 1.1 Synopsis	The screening days were revised from "between Day -14 and -2" to "between Day -28 and -2."	
Section 4.1.1 Screening	Screening days were revised from "between Day -14 and -2" to "between Day -28 and -2."	
Section 2.1 Study Rationale	The following text was added: The COVID-19 public health emergency has disrupted the conduct of clinical research throughout the world. At Endo Pharmaceuticals Inc. (Endo), ensuring the safety of clinical study participants is our primary concern. In	Language was developed to clarify how the Sponsor will proceed during the COVID-19 Public Health Emergency.

Section No. and Name	Description of Change	Brief Rationale
	addition, the integrity of data obtained from clinical trials must be ensured. In order to ensure subject safety and protect data integrity, Endo, in accordance with the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (March 2020, updated 02 July 2020), will allow virtual visits for safety assessments. During a potential travel restriction/lockdown due to COVID-19, subjects enrolled in the study may experience a delay or cancellation of important site visits that could impact serum testosterone levels and delay or affect the required testosterone replacement. To avoid any potential delay or disruption in the testosterone replacement therapy of those subjects, as our commitment toward every subject's well-being, Endo may decide to temporarily delay the enrollment of the subjects into any of the arms of the protocol. In addition, any subjects affected by the health emergency will be allowed to continue in the study and complete remaining assessments when the investigational sites re-open as follows: • 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 Section 1.2.	
Section 5.2 Exclusion Criteria, Exclusion Criterion #21	Was modified to: 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).	Subjects who were taking prescribed medication were having positive urine drug screen testing given the components of these medication, (ie, Adderall for ADD showed positive for amphetamine).

Section No. and Name	Description of Change	Brief Rationale
Section 5.5 Screen Failures	The last paragraph was deleted and replaced with: A subject who does not meet all of the eligibility criteria and is considered a screen failure may be rescreened once. If a subject rescreens within 30 days of their original screening date, assessments from the initial screening period may be used as long as they are considered to be valid and within protocol entry criteria. Any abnormal assessments must be repeated. The period from the start of rescreening related procedures to the study treatment must not exceed 28 days.	Rescreening language has been added to allow the assessments performed in the initial screen to be used if no more than 30 days have passed since the assessments were performed and the assessments are considered valid.
Section 8.1 Safety Assessments	The following paragraph was added: In order to ensure subject safety and protect data integrity, Endo, in accordance with the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (March 2020, updated 02 July 2020), will allow virtual visits for safety assessments. During a potential travel restriction/lockdown due to COVID-19, subjects enrolled in the study may experience a delay or cancellation of important site visits that could impact serum testosterone levels and delay or affect the required testosterone replacement. To avoid any potential delay or disruption in the testosterone replacement therapy of those subjects, as our commitment toward every subject's well-being, Endo may decide to temporarily delay the enrollment of the subjects into any of the arms of the protocol. In addition, should subjects be affected by the health emergency, they will be allowed to continue in the study and complete remaining assessments when the investigational sites re-open.	Language was developed to clarify how the Sponsor will proceed during the COVID-19 Public Health Emergency.

Section No. and Name	Description of Change	Brief Rationale
Section 8.1.5 Vital Signs	The **highlighted** text was added: **Subjects receiving the Aveed injection will have vital signs 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. 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.	To clarify that vital signs must be taken before Aveed injection.
Section 9.1 Sample Size Determination	ABPM Population was changed to **Full Analysis Set**.	Changed to clarify Sample Sets
Section 9.2 Analysis Populations	This section was updated to the following: Four analysis populations will be considered in the study: the Safety Population, the Intent-to-Treat Population (ITT), the Full Analysis Set (FAS), and the ABPM Population. • Safety Population: will include all subjects who receive at least 1 dose/injection of study treatment. All safety analyses will be based on the Safety Population. • Intent-to-Treat Population: (ITT): will include all randomized subjects who have at least 1 dose/injection of study medication. Sensitivity analysis for primary and secondary efficacy analysis will be based on this population to assess the effect due to study discontinuation. • Full Analysis Set (FAS): will include all ITT subjects with valid baseline and EoS ABPM assessments, and. All primary and secondary efficacy analysis will be based on the ABPM Population. • ABPM Population: will include all FAS subjects with at least 85% compliance to treatment during the study. All primary and secondary efficacy analysis will be based on the ABPM Population.	Two analysis sets were added to the analysis populations.

Section No. and Name	Description of Change	Brief Rationale
Section 9.3.1.3 Sensitivity Analysis	This section has been added: 9.3.1.3. Sensitivity Analysis Two types of sensitivity analysis will be performed: 1) primary and secondary analysis based on ABPM population, 2) primary and secondary analysis based on ITT population to account for missing data due to study discontinuation.	Added to clarify sensitivity analysis.

Overall Rationale for the Amendment 1

The primary purpose of this amendment was to separate descriptions of treatment with testosterone gel (Fortesta/Testim) from descriptions and procedures of treatment with testosterone solution for injection (Aveed). This change was to clarify both the schedule of treatment of study drugs and the procedures for each arm of the study. Amendment 1 was incorporated into the protocol on 19 March 2020.

Minor changes throughout the protocol amendment included wording changes for clarity, correction of minor typographical errors and revision of abbreviations.

Major changes are listed below.

Section No. and Name	Description of Change	Brief Rationale
Protocol Amendment Summary of Changes	Summary of Changes Added	Added with Amendment 1
Abbreviations throughout Amendment	Abbreviations updated and standardized	
Section 1.1 Synopsis Section 4.1.3 Treatment	Key Inclusion Criteria added	Added to clarify overall study design description
Section 1.1 Synopsis Section 4.1.3 Treatment	Treatment description for Aveed separated from treatment description for Fortesta/Testim	Added to clarify the differences in treatment days and procedures between testosterone gel (Fortesta/Testim) and injection (Aveed) Timing of ABPM analysis for Aveed was revised to Day 100 to align with item 3 (Advice/ Information Request dated May 24, 2019)
Section 1.1 Synopsis Section 4.1.5 Ambulatory Blood Pressure Monitoring (End of Study)	Description of End of Study procedures for Fortesta/Testim separated from End of Study for Aveed	
Section 1.2 Schedule of Activities, Table 1 and Table 2	The Schedule of Activities table has been separated into a table for Fortesta/Testim and a second table for Aveed	Tables separated to clarify the differences in treatment days and procedures between testosterone gel (Fortesta/Testim) and injection (Aveed) Timing of ABPM analysis for Aveed was revised to Day 100 to align with item 3 (Advice/ Information Request dated May 24, 2019)
Section 5.2 Subject Exclusion Criteria	Reorganized for clarity	

Section No. and Name	Description of Change	Brief Rationale
Section 5.5 Screen Failures	Reworded for clarity	
Section 6.1 Treatment Administration, Table 3	Updated to clarify timing of treatment for each treatment	
Section 6.2 Study Treatment Preparation/Handling/Storage/ Accountability Section 6.4 Study Treatment Compliance	Added information on study drug accountability monitoring – tubes and canisters must be returned at each visit.	
Section 8.1.5 Vital Signs	The procedure for taking vital signs was expanded	
Section 8.2.5 Pregnancy	Procedures regarding pregnancies in the partners of study participants were clarified	

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LIST OF ABBREVIATIONS

Abbreviation or Special Term	Explanation
ABPM	Ambulatory blood pressure monitoring
AE	Adverse event
BP	Blood pressure
CFR	Code of Federal Regulations
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
EoS	End-of-study
FDA	Food and Drug Administration
GCP	Good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
ID	Identification
IEC	Independent ethics committee
IRB	Institutional review board
IRT	Interactive response technology
LH	Luteinizing hormone
MAP	Mean arterial pressure
PI	Prescribing information
PP	Pulse pressure
REMS	Risk evaluation and mitigation strategies
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SoA	Schedule of activities
TEAE	Treatment-emergent adverse event
TRT	Testosterone replacement therapy

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Marketed Products: AVEED® (testosterone undecanoate) injection, TESTIM® (testosterone gel), FORTESTA® (testosterone) Gel

Name of Active Ingredient: Testosterone

Title of Study: 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 Administration With Marketed Testosterone Products

Principal Investigator: (To be determined)

Study Period: Date first subject enrolled: June 2020 Estimated date last subject completed: December 2022	**Phase of Development:** 4

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 obtained during treatment. • Change from baseline over time (hourly average) by nominal clock time and time after dose in MAP, SBP, DBP, PP, and heart rate. • Percent of subjects with new antihypertensive medications. • Percent of subjects with dose increases in antihypertensive medications.

Overall 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 BP after 16 weeks of continuous treatment with marketed testosterone products.

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Marketed Products: AVEED® (testosterone undecanoate) injection, TESTIM® (testosterone gel), FORTESTA® (testosterone) Gel

Name of Active Ingredient: Testosterone

A total of approximately 618 hypogonadal males will be enrolled across the 3 treatment arms of this study. Subjects currently with controlled hypertension and without hypertension will be enrolled. The study will consist of a screening phase, followed by a 24-hour ambulatory blood pressure monitoring (ABPM) phase (baseline). After baseline BP has been monitored, subjects will be randomly assigned to 1 of 3 treatment arms.

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, buccal, nasal, 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.

Screening will take place between Day -28 and Day -2. Screening assessments will include (but are not limited to) informed consent, serum testosterone levels, physical examination, 12-lead electrocardiogram (ECG), vital signs, and clinical laboratory tests. After all assessments are completed, each subject's eligibility will be evaluated. Subjects found eligible will be instructed to return to the study center on Day -1 for the activities described in the Schedule of Activities (SoA).

Blood samples will be collected on Day -1 for 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).

After the 24-hour ABPM is read and determined to be valid (Day 2), each subject will be randomly assigned to 1 of the 3 treatment arms:

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

Fortesta and Testim subjects will be administered the allotted study drug and start application of the study drug on Day 2. Subjects will be instructed not to shower, wash, and/or swim within two hours after daily study drug application and will be provided with instructions to continue applying/ administering topically the Fortesta or Testim study drug according to the approved PI. Aveed subjects will receive an intramuscular injection on Day 2, Day 30 (± 3 days), and Day 100 (± 3 days). For more information on study treatments, see the Study Operations Manual.

Name of Sponsor/Company: Endo Pharmaceuticals Inc.
Name of Marketed Products: AVEED® (testosterone undecanoate) injection, TESTIM® (testosterone gel), FORTESTA® (testosterone) Gel
Name of Active Ingredient: Testosterone
Fortesta and Testim subjects will be instructed to visit the clinic during the Treatment Follow-up Phase on Day 16, Day 37, Day 67, and Day 97 (± 3 days). During each of these visits, serum testosterone levels will be taken at the designated times (2 hours prior to Testim application and 2 hours after Fortesta application) followed by instructions for titrating dose accordingly if applicable. For subjects on the Fortesta arm, if further titration is required after the Follow-up Visit on Day 37, the investigator should refer to the PI for information on when to schedule subsequent follow up visits. The daily dose of the study drug will be titrated for each subject, according to approved dosage and administration instructions, until the circulating testosterone concentrations of the subject reaches normal concentrations (300-1000 ng/dL). The appropriate amount of study drug will be dispensed to subjects to last until the next follow-up visit. However, if titration is needed, subjects may need to return to the clinic in between scheduled follow-up visits for additional drug supply. If additional visits are required during the Treatment Follow-up Phase, they may occur as Unscheduled Visits. Subjects will follow the same instructions as previously outlined for any Unscheduled Visits as were followed during the Treatment Follow-up Phase. Laboratory evaluations should be performed as needed during unscheduled visits. Unscheduled visits may occur as necessary for the Aveed subjects. Fortesta and Testim subjects will be instructed to visit the study center on Day 113 (± 3 days) for blood collection for serum testosterone determination and again on Day 114 to be fitted with the ABPM device in addition to the other EoS assessments as described in the Testim and Fortesta SoA. A 24-hour ambulatory blood pressure recorder machine will be attached to the subject's arm (using the same arm as for baseline), at bicep level. The machine will be set to measure BP every 30 minutes for the next 24 hours. The 24-hour ambulatory blood pressure recorder machine must be returned to the study site by the subject on the following day (Day 115). Aveed subjects will be instructed to visit the study center on Day 30 (± 3 days), and Day 100 (± 3 days) for intramuscular injections and 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 in addition to completing the other assessments as listed in the Aveed SoA. A 24-hour ambulatory blood pressure recorder machine will be attached to the subject's arm (using the same arm as the baseline), at bicep level. The machine will be set to measure BP every 30 minutes for the next 24 hours. On Day 108 the 24-hour ambulatory blood pressure recorder machine must be returned to the study site by the subject. If a subject is terminated early, an early termination 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. EoS activities/assessments are listed in the SoA.
Disclosure Statement: This is an open-label 3 treatment-arm study in 3 different marketed testosterone treatments.
Number of Subjects (planned): Approximately 618 subjects will be enrolled across the 3 treatment arms.
Treatment Groups and Duration: All subjects will receive 1 of 3 testosterone treatments. Each treatment will be administered according to the applicable PI.
Data Monitoring Committee: No monitoring committees will be used for this study.

1.2. Schedule of Activities

Table 1: Schedule of Activities – Testim and Fortesta

Procedures	Screening Phase Day -28 to -2	Baseline			Treatment Follow-up Visits[a]	End-of-Study/Early Termination		
		Day -1	Visit 1 Day 1	Return Visit Day 2	Visits 2a to 2d[b] Days 16, 37, 67, and 97	Day 113 (± 3 days)	EoS Visit Day 114 (± 3 days)	Return Visit Day 115
Informed consent	X							
Inclusion/exclusion	X[c]		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) [d]	X		X	X	X		X	X
12-lead ECG	X						X	
International Prostate Symptom Score (IPSS)[e]	X							
Digital rectal examination of the prostate	X							
Alcohol and tobacco screen	X							
Clinical laboratory[f]	X							
Serum testosterone	X[g]	X			X[h]	X[h]		
24-hour ABPM			X[i]				Xi	
Confirm valid ABPM session[j]				X				X

Table 1: 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		
		Day -1	Visit 1 Day 1	Return Visit Day 2	Visits 2a to 2d[b] Days 16, 37, 67, and 97	Day 113 (± 3 days)	EoS Visit Day 114 (± 3 days)	Return Visit Day 115
AEs/SAEs	X	X	X	X	X	X	X	X
TREATMENT								
Randomization[k]				X				
Dispense Study Drug[l]				X	X			
Collect Study Drug					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] Testosterone samples collected at Screening will be used for evaluating study inclusion.

[d] 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.

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

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

[g] 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).

[h] 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.

[i] Onsite device activation.

[j] 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.

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

[l] 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 2: Schedule of Activities – Aveed (Testosterone Undecanoate Injection)

Procedures	Screening Phase Day -28 to -2	Baseline			Treatment Visits (± 3 days)		End-of-Study/Early Termination		
		Day -1	Visit 1 Day 1	Return Visit Day 2	Study Visit Day 30	Study Visit Day 100	Day 106 (± 3 days)	EoS Visit Day 107 (± 3 days)	Return Visit Day 108
Informed consent	X								
Inclusion/exclusion	X[d]		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	X[e]	X					X		
24-hour ABPM			X[f]					X[f]	

Table 2: 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		
		Day -1	Visit 1 Day 1	Return Visit Day 2	Study Visit Day 30	Study Visit Day 100	Day 106 (± 3 days)	EoS Visit Day 107 (± 3 days)	Return Visit Day 108
Confirm valid ABPM session[g]				X					X
Randomization[h]				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] Testosterone samples collected at Screening will be used for evaluating study inclusion.

[e] 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).

[f] Onsite device activation.

[g] 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.

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

2. INTRODUCTION

2.1. Study Rationale

This study will allow for a comparison of the safety profiles of 3 different marketed drugs over 16 weeks of treatment.

The COVID-19 public health emergency has disrupted the conduct of clinical research throughout the world. At Endo Pharmaceuticals Inc. (Endo), ensuring the safety of clinical study participants is our primary concern. In addition, the integrity of data obtained from clinical trials must be ensured.

In order to ensure subject safety and protect data integrity, Endo, in accordance with the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (March 2020, updated 02 July 2020), will allow virtual visits for safety assessments. During a potential travel restriction/lockdown due to COVID-19, subjects enrolled in the study may experience a delay or cancellation of important site visits that could impact serum testosterone levels and delay or affect the required testosterone replacement. To avoid any potential delay or disruption in the testosterone replacement therapy of those subjects, as our commitment toward every subject's well-being, Endo may decide to temporarily delay the enrollment of the subjects into any of the arms of the protocol.

In addition, any subjects affected by the health emergency will be allowed to continue in the study and complete remaining assessments when the investigational sites re-open as follows:

- 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 Section 1.2.

2.2. Background

Testosterone is the principal androgen produced by the male testes (Rommerts, 2004). It is involved in several developmental and physiological processes, including virilization of the male reproductive tract, skeletal muscle development, growth in stature, male pattern hair growth at the onset of puberty, spermatogenesis in adults and control of the gonadotropic functions of the pituitary by down-regulating the synthesis of luteinizing hormone (LH). It also plays a major role in male sexual behavior.

Male hypogonadism is the result of inadequate production of testosterone by the Leydig cells of the testes (Odell and Swerdloff, 1978). Hypogonadism is reflected by serum concentrations of testosterone of < 300 ng/dL, with no discernible diurnal pattern (Surampudi et al, 2014). The etiology of hypogonadism may be primary or secondary. Primary hypogonadism is associated with dysfunction in the testes. Idiopathic primary testicular failure affects approximately 5% of the male population. Secondary hypogonadism is due to inadequate hormonal stimulation of functionally normal testes. The causes may be of hypothalamic or pituitary origin, including gonadotropin-releasing hormone deficiencies, isolated follicle-stimulating hormone or LH deficiencies, acquired gonadotropin deficiencies, prolactin secreting tumors, severe systemic illness, uremia, and hemochromatosis.

The treatment of males with primary, and in some cases, secondary hypogonadism includes administration of testosterone. Numerous clinical studies have confirmed the efficacy of testosterone in the treatment of hypogonadism (Thirumalai et al, 2017). The safety of testosterone administration is well established (Lawrence et al, 2017; Reaven, 1995; Malkin et al, 2003). Clinical studies and literature reports have established the physiological and pharmacological effects and safety, even of large doses, of testosterone in both hypogonadal and eugonadal men (Ruige et al, 2001).

Recently, however, there has been growing concern over the use of testosterone therapy and the increased risk of cardiovascular disease (Clavell-Hernandez and Wang, 2018). In a cohort study performed by Loo (Loo et al, 2019),evidence suggested that during the first 2 years of testosterone treatment, men with low testosterone levels were more likely to experience cardiovascular events such as ischemic stroke, transient ischemic attacks (TIAs), and myocardial infarction. Other studies, however, have found that testosterone replacement therapy (TRT) used to return testosterone to normal levels in hypogonadal males may actually have a beneficial effect on the cardiovascular system (Elagizi et al, 2018). Given the conflicting nature of this evidence, the increasing use of testosterone therapy has necessitated a re-evaluation of the safety of testosterone products. One avenue for the evaluation of cardiovascular safety during testosterone therapy is ambulatory blood pressure monitoring (ABPM) in subjects receiving testosterone treatment.

ABPM is used to monitor BP over 24-hours in order to reveal shifts in BP levels that occur at various times during the day. According to the European Society of Hypertension (O'Brien et al, 2013), some of the benefits of frequent BP measurements during the day include the ability to monitor BP during sleep, identification of 'white-coat' and masked hypertension, and the variation of subject BP during a 24-hour cycle. Of particular importance, ABPM, using a validated device coupled with subject training, allows BP monitoring in the home with measurements every 30 minutes, thereby providing a much more accurate picture of the subject's BP at different time points.

This study is designed to evaluate the effects of 3 different approved testosterone products on the ambulatory BP of hypogonadal males after 16 weeks of therapy.

2.3. Risk/Benefit Assessment

Adverse events (AEs) associated with TRT include gynecomastia, fatigue, priapism, weight gain, decreased high density lipoprotein (HDL) cholesterol, increased prostate size, difficulty in urination, and erythrocytosis (increased hemoglobin and/or hematocrit). Androgens are contraindicated in men with carcinoma of the breast or a history of primary hepatic carcinoma, known or suspected carcinoma of the prostate, nephrotic syndrome, hypercalcemia, and must be used cautiously in men with prostatic hypertrophy.

Hypogonadism has been treated with administration of exogenous testosterone since it was synthesized some 60 years ago. Testosterone is approved by the US Food and Drug Administration (FDA) as replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone. Testosterone is currently available in oral formulation, injectable depot solution, pellet implants, transdermal patches, topical gels, and buccal tablets. High dose oral formulations (testosterone esters) given for prolonged periods are associated with an increased incidence of liver disease, including cancer. Depot solutions are administered

relatively frequently and are considered painful injections. Another issue associated with the depot formulation is the mood swings that are produced as a result of the sustained supraphysiologic concentrations of testosterone that occur immediately after injection and lower than normal concentrations during the time period (a few days) prior to the next scheduled injection. Transdermal patches are often associated with a high incidence of inflammation at the site of application and pellet implants can result in rejection and infection. Since marked first pass metabolic inactivation of testosterone occurs in the liver after oral administration, testosterone esters by intramuscular administration have until recently been the mainstay of replacement therapy. However, significant amounts of testosterone are absorbed and enter the systemic circulation when applied to the skin in an appropriate vehicle. This observation was the basis for developing testosterone patches to deliver the hormone to scrotal and non-scrotal skin, and most recently by a topical testosterone gel (1%). Testosterone 2% gel is currently approved in 20 European countries.

More detailed information about the known and expected benefit, risks, and reasonably expected AEs can be found in the Package Inserts for each treatment in this study. Additional information will be provided to subjects receiving Aveed in accordance with the approved risk evaluation and mitigation strategies.

3. OBJECTIVES AND ENDPOINTS

3.1. Study Objective(s)/Endpoint(s)

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 obtained during treatment. • Change from baseline over time (hourly average) by nominal clock time and time after dose in MAP, SBP, DBP, PP, and heart rate. • Percent of subjects with new antihypertensive medications. • Percent of subjects with dose increases in antihypertensive medications.

4. STUDY DESIGN

4.1. Overall 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 BP after 16 weeks of continuous treatment with marketed testosterone products.

A total of approximately 618 hypogonadal males will be enrolled across the 3 treatment arms in this study. Subjects currently with and without hypertension will be enrolled. The study will consist of a screening phase, followed by a 24-hour ABPM phase (baseline). After a valid 24-hour ABPM has been confirmed, subjects will be randomly assigned to 1 of 3 treatment arms.

4.1.1. Screening

Screening will take place on multiple days between Day -28 and Day -2. Informed consent will be obtained from all subjects prior to any screening assessments. Screening assessments will include (but are not limited to) informed consent, serum testosterone levels, physical examination, 12-lead electrocardiogram (ECG), vital signs, and clinical laboratory tests. After all assessments are completed, each subject's eligibility will be evaluated. Subjects found eligible

will be instructed to return to the study center on Day -1 for the activities described in the Schedule of Activities (SoA).

4.1.2. Ambulatory Blood Pressure Monitoring (24 Hour)

Blood samples will be collected on Day -1 for 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).

In this clinical trial, an FDA cleared ABPM device will be used that meets the latest Association for the Advancement of Medical Instrumentation, European Society of Hypertension standards and also will have a British Hypertension Society A/A rating. The same brand of ABPM device will be used for every subject enrolled into the trial and each subject will use the same device at both the Day 1 Visit and as applicable, the EoS or Early Termination visit.

In order to receive study drug on Day 2, the baseline 24-hour ABPM reading must be reviewed by the investigator (or qualified designee) in real time and considered 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 or at the end of study visit the ABPM session may be repeated once in order to obtain a valid ABPM session.

4.1.3. Treatment

After ABPM is complete (Day 2) and determined by the investigator to be valid, each subject will be randomly assigned to 1 of the 3 treatment arms:

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

Fortesta and Testim subjects will be administered the allotted study drug and start application of the study drug on Day 2. Subjects will be instructed not to shower, wash, and/or swim within two hours after daily study drug application and will be provided with instructions to continue applying/administering topically the Fortesta or Testim study drug according to the approved PI. Aveed subjects will receive an intramuscular injection on Day 2, Day 30 (± 3 days), and Day 100 (± 3 days). For more information on study treatments, see the Study Operations Manual and Table 3.

Fortesta and Testim subjects will be instructed to visit the clinic during the Treatment Follow-up Phase on Day 16, Day 37, Day 67, and Day 97 (± 3 days). During each of these visits, serum testosterone levels will be taken at the designated times (2 hours prior to Testim application and 2 hours after Fortesta application) followed by instructions for titrating dose accordingly if applicable. For subjects on the Fortesta arm, if further titration is required after the Follow-up Visit on Day 37, the investigator should refer to the PI for information on when subsequent

follow-up visits should be scheduled. The daily dose of the study drug will be titrated for each subject, according to approved dosage and administration instructions, until the circulating testosterone concentrations of the subject reaches normal concentrations (300-1000 ng/dL). The appropriate amount of study drug will be dispensed to each subject to last until the next follow-up visit. However, if titration is needed, subjects may need to return to the clinic in between scheduled follow-up visits for additional drug supply. If additional visits are required during the Treatment Follow-up Phase, they may be occur as Unscheduled Visits. Subjects will follow the same instructions as previously outlined for any Unscheduled Visits during the Treatment Follow-up Phase. 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 (for more information on titration and dose treatment scheduling, see the Pharmacy Manual). Unscheduled visits may occur as necessary for the Aveed subjects.

4.1.4. Interim Evaluation

Not applicable.

4.1.5. Ambulatory Blood Pressure Monitoring (End of Study)

4.1.5.1. Testim and Fortesta Treatment Arm

Subjects will be instructed to visit the study center on Day 113 (± 3 days) for a serum testosterone assessment, and again on Day 114 (± 3 days) to be fitted with the ABPM device in addition to completing the other EoS assessments as listed in the Testim and Fortesta SoA. Subjects will apply the study drug as usual at home before the Day 114 visit. A 24-hour ambulatory blood pressure recorder machine will be attached to the subject's arm (using the same arm as for baseline), at bicep level. The machine will be set to measure BP every 30 minutes for the next 24 hours. On Day 115 the 24-hour ambulatory blood pressure recorder machine must be returned to the study site by the subject. 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.

4.1.5.2. Aveed Treatment Arm

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 (± 3 days) to be fitted with the ABPM device in addition to completing the other assessments as listed in the Aveed SoA. A 24-hour ambulatory blood pressure recorder machine will be attached to the subject's arm (using the same arm as the baseline), at bicep level. The machine will be set to measure BP every 30 minutes for the next 24 hours. On Day 108 the 24-hour ambulatory blood pressure recorder machine must be returned to the study site by the subject. 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 early termination 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. EoS activities/assessments are listed in the SoA.

4.1.6. Study Duration

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

4.2. Scientific Rationale for the Study Design

This is an open-label exploratory study designed to investigate the effect of testosterone treatment on BP in hypogonadal men.

4.3. Justification for Dose

All treatments in this study are with approved, marketed drugs, using the approved doses found in the PI.

4.4. End-of-Study Definition

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

The EoS is defined as the completion of the final assessment for the last subject enrolled in the trial.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Subject 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, buccal, nasal, 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 Section 10.1.3.

5.2. Subject 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, 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 and is judged by the investigator not to substantially increase risk to participate in the study and, will not interfere with the subject's participation in the study, the subject may be included, with documented approval from 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 ≥ 19. A clinically significant digital rectal examination of the prostate or clinically significant elevated serum prostate-specific antigen levels (> 4.0 ng/mL).
    b. Known or suspected carcinoma of the breast. Participant has cancer, or a history of relapse (except for basal cell carcinoma of the skin) within the previous 5 years.
    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 QTcF ≥ 450 ms.
24. Has any other condition that, in the investigator's opinion, might indicate the subject to be unsuitable for the study.

5.3. 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 randomized.

5.4. Lifestyle Considerations

Subjects should not donate blood while participating in this study and for 30 days after the last investigational treatment.

5.5. Screen Failures

Screen failures are defined as subjects who consent to participate in this study but are not subsequently randomized.

Subjects who do not meet all of the eligibility criteria prior to randomization will be deemed screen failures. The following information must be recorded for all subjects who are screen failures:

- Demography (age, gender, race/ethnicity).
- Reason for screen failure.
- Which eligibility criterion was not met.
- Any AE experienced by the subject.

A subject who does not meet all of the eligibility criteria and is considered a screen failure may be rescreened once. If a subject rescreens within 30 days of their original screening date, assessments from the initial screening period may be used as long as they are considered to be

valid and within protocol entry criteria. Any abnormal assessments must be repeated. The period from the start of rescreening related procedures to the study treatment must not exceed 28 days.

6. STUDY TREATMENT

Study treatment is defined as any investigational treatment, marketed products, placebo, or device intended to be administered to a study subject according to the study protocol.

6.1. Treatment Administration

Table 3: 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	IM Injection Injection site: gluteus medius muscle	Topical Apply to upper inner thighs	Topical Apply to shoulders or upper arms
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Product will be provided in glass vials. Each vial will be labeled per country requirements.	Product will be provided in metered pump. Each pump will be labeled per country requirements.	Product will be provided in 50 mg tubes. Each tube will be labeled per country requirements.

[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.

6.2. Study Treatment Preparation/Handling/Storage/Accountability

The investigator or designee will confirm that appropriate temperature control conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved prior to study treatment administration.

The study treatment will be maintained in a monitored, environmentally controlled (in accordance with treatment labeling), secure, locked area with restricted access at the study site in compliance with standards of the Drug Enforcement Agency (DEA) for Schedule III drugs.

Only subjects enrolled in the study will receive study treatment and only authorized study staff will dispense study treatment.

In accordance with the International Council for Harmonisation (ICH) requirements, at all times the investigator must be able to account for all study treatment furnished to the study site. An accountability record must be maintained for this purpose. The investigator must maintain accurate records indicating dates and quantity of study treatment received, to whom it was administered (subject-by-subject accounting) and accounts of any study treatment accidentally or

deliberately destroyed. All unused study treatment not involved in immediate subject treatment must be maintained under locked, temperature-controlled storage at the study site. At each visit subjects must return all used and unused study drug tubes and canisters to the study center.

Investigators should refer to the Pharmacy Manual for complete information regarding preparation, handling, storage, and accountability of study treatment.

6.3. Measures to Minimize Bias

This is an open label study; however, the specific treatment taken by each subject will be assigned using interactive response technology (IRT). Subjects will be randomized to receive study treatment in a 1:1:1 ratio.

6.3.1. Interactive Response Technology

The investigator or designee will utilize an IRT system to register subjects at screening. Each subject's unique identification (ID) number will be assigned by the IRT system and will be used to identify the subject for the duration of the study within all systems and documentation. If the subject is not eligible to receive study treatment, or should discontinue from the study, the subject ID number will not be reassigned to another subject. Specific instructions for the use of the IRT system will be included in an IRT User Manual.

The investigator must maintain a subject master log linking the subject ID to the subject's name. The investigator must follow all applicable privacy laws in order to protect a subject's privacy and confidentiality. Information that could identify a subject must be masked on material received by the sponsor.

6.4. 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. Subjects will be instructed to bring all used and unused tubes and canisters each time they return to the clinic.

Study drug compliance during each study visit/any period 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.

Accidental or intentional overdoses should be reported to the sponsor/designee promptly (see Section 8.3).

6.5. Prior and Concomitant Medications and Procedures

The start and stop date, dose, unit, frequency, route of administration, and indication for all prior (taken within the 30 days prior to the Screening Visit) and concomitant (taken from the Screening Visit through the EoS/Early Termination Visit) medications and nondrug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, etc) received will be recorded.

In addition, all prior treatments for the disease/condition under study administered in the previous 5 years will be recorded with start and stop date, dose, unit, frequency and route of administration.

6.5.1. Prohibited Medications and Procedures

Use of known inhibitors (eg, ketoconazole) or inducers (eg, dexamethasone, phenytoin, rifampin, carbamazepine) of CYP3A will be prohibited in this study.

If any prohibited medication is taken during the study, all pertinent information will be recorded. The designated study Medical Monitor must be informed immediately so the sponsor may determine whether to continue the subject in the study.

7. DISCONTINUATION FROM STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

Subjects may be discontinued from the study for the following reasons, if deemed appropriate by the sponsor or investigator:

- Entered the study in violation of this protocol.
- Safety reasons as judged by the investigator and/or sponsor.
- Severe non-compliance to the protocol as judged by the investigator and/or sponsor.
- Required the use of an unacceptable concomitant medication (see Section 6.5).
- Withdrawal of informed consent; any subject who withdraws consent as a result of an AE, regardless of severity or investigator's opinion, must be reported as a discontinuation due to an AE.
- In the investigator's opinion, it is not in the subject's best interest to continue.
- Sponsor decision.

Subjects who discontinue or are withdrawn from study treatment for any reason, will be encouraged to complete the Early Termination visit 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 date of and reason for study treatment discontinuation will be recorded. Subjects will be encouraged to continue in the study for safety and complete all assessments in the SOA for their respective treatment arm (except for study drug administration) and final ABPM measurements.

If a clinically significant cardiac finding is identified (including but not limited to changes from baseline in QT interval corrected using Fridericia's Formula [QTcF]) after the start of study treatment, the investigator or a qualified designee will determine if the subject can continue in the study and if any change in management is needed.

Subjects who discontinue from study treatment at any time after the first dose of study drug will not be replaced.

7.2. Subject Discontinuation/Withdrawal From the Study

Subjects may withdraw from the study at any time at their own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. The date of and reason for withdrawal will be recorded.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such withdrawal of consent. If a subject withdraws from the study, the subject may request destruction of any samples taken and request the samples not be tested. The investigator must document this in the site study records.

A subject may be discontinued from the study for the following medical or administrative reasons:

- Withdrawal by subject (reason must be specified).
- An AE.
- Death.
- A protocol violation (reason must be specified, for example: lack of compliance, use of a prohibited concomitant medication, etc).
- The subject was lost to follow-up.
- Other reasons (reason must be specified, for example: the subject moved, investigator decision, pregnancy of partner [for subjects using Testim or Fortesta] sponsor decision to terminate trial, etc).

If a subject discontinues from the study, all EoS procedures should be conducted as detailed in the SoA. The investigator should request that the subject agree to 24-hour ABPM measurement. The date a subject discontinues and the reason for discontinuation will be recorded in the source documentation and electronic case report form (eCRF). If, however, a subject withdraws consent, no additional procedures are required. This information should be recorded in the source documentation and the eCRF.

7.3. Lost to Follow-up

A subject will be considered lost to follow-up if the subject repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and to ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls, and if necessary, a certified letter to the subject's last known mailing address; or local equivalent methods). These attempts will be documented.

- Should the subject continue to be unreachable, the subject will be considered to have withdrawn from the study.

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

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 1 and Table 2). Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. Protocol waivers or exemptions are not allowed.

Urgent safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue study treatment and/or be withdrawn from the study.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screen failure, as applicable.

Procedures conducted as part of the subject's routine clinical management and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each subject over the duration of the study, including extra assessments that may be required, will not exceed 100 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Safety Assessments

All safety assessments will be performed at the time outlined in the SoA. Additional (unscheduled) safety assessments may be performed as needed.

In order to ensure subject safety and protect data integrity, Endo, in accordance with the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (March 2020, updated 02 July 2020), will allow virtual visits for safety assessments. During a potential travel restriction/lockdown due to COVID-19, subjects enrolled in the study may experience a delay or cancellation of important site visits that could impact serum testosterone levels and delay or affect the required testosterone replacement. To avoid any potential delay or disruption in the testosterone replacement therapy of those subjects, as our commitment toward every subject's well-being, Endo may decide to temporarily delay the enrollment of the subjects into any of the arms of the protocol. In addition, should subjects be affected by the health emergency, they will be allowed to continue in the study and complete remaining assessments when the investigational sites re-open.

8.1.1. Serum Testosterone Assessment

Blood samples of approximately 100 mL will be collected in this study for analysis of serum testosterone from all subjects participating in the study at the times outlined in the SoA (Table 1 and Table 2). During the Screening Period, 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). Testosterone samples collected during the Screening Period will be used for study inclusion. Testosterone samples collected at Day -1 will be used as a baseline for the study. The date and time of each sample collection will be recorded. Detailed instructions of the collection, processing, storage, and shipment of these samples will be provided in a separate laboratory manual.

8.1.2. Medical and Surgical History

Medical and surgical history will be obtained during the screening period. 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 will be recorded.

History of tobacco and alcohol use (never, current, former) will also be collected at screening.

8.1.3. Physical Examination

The complete 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.

All examinations will be performed by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations. The investigator will review all physical exam findings for clinical significance. Any physical exam finding meeting the investigator's or sponsor's criteria for clinical significance will be recorded as an AE or serious adverse event (SAE) as appropriate.

8.1.4. Height and Weight

Height will be collected at screening only. Weight will be collected as outlined in the SoA. Any change from the Screening Visit in subject weight that is considered by the investigator to be clinically significant will be recorded as an AE (or SAE, if appropriate).

8.1.5. Vital Signs

Subjects receiving the Aveed injection will have vital signs 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. 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.

The investigator will review all vital sign values for clinical significance. Any vital sign value meeting the investigator's or sponsor's criteria for clinical significance will be recorded as an AE (or SAE, if appropriate).

8.1.6. Electrocardiogram

A 12-lead ECG recording will be conducted at the times indicated on the SoA. The subject should be in a supine position for at least 5 minutes before the recording is conducted. Lead position will be that of a standard 12-lead ECG; no additional or special lead placements will be necessary. The ECG recording should include a minimum of 5 heart cycles (beats).

If the ECG report shows QT prolongation with QTcF $\geq$ 450 ms, the investigator should repeat the ECG within 1 hour. If the initial findings are confirmed, the investigator should exclude the subject from study participation.

The investigator will review all other ECG results for clinical significance. Any ECG result meeting the investigator's criteria for clinical significance will be recorded as an AE (or SAE, if appropriate).

8.1.7. Clinical Laboratory Determinations

Clinical laboratory tests will be conducted according to the SoA. Required clinical laboratory tests are outlined in Section 10.2. Clinical laboratory tests will be performed by a designated central laboratory. The study sites will be provided with instructions on specimen collection, preparation, packaging and transport. The results of the tests will be returned to the investigational sites.

Samples for laboratory testing may be collected under fasted or nonfasted conditions. Fasting early morning samples are preferred, but a random daytime sample is acceptable. The date and time of the sample collection must be documented on the laboratory report. The investigator must review and sign laboratory reports and document the clinical significance of each laboratory abnormality. New clinically significant laboratory abnormalities or clinically significant changes in laboratory values will be reported as AEs (or SAEs, if appropriate).

Clinical laboratory test data will be reviewed by the investigator, or designee, and additional clinical laboratory tests may be ordered at his/her discretion (eg, if the results of any clinical laboratory test falls outside the reference range or clinical symptoms necessitate additional testing to ensure safety). Any additional testing will be performed by the designated central laboratory or local laboratory if needed to ensure subject safety.

8.2. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.3.

All AEs, including both observed or volunteered problems, complaints, signs or symptoms must be recorded, regardless of whether associated with the use of study treatment. 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. The AE should be recorded in standard medical terminology when possible.

8.2.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All SAEs and AEs will be collected by the investigator from the time the ICF is signed through the Day 115 EoS visit (Testim and Fortesta) and Day 108 (Aveed); or for 28 days after the last dose of study treatment for those who terminate early; this will include any AEs that are ongoing at the time of study completion/termination. All ongoing AEs must be followed until resolution or for 28 days after the subject's last study treatment, whichever comes first.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

The investigator is not obligated to actively seek AEs and SAEs after conclusion of subject study participation. However, if the investigator learns of any SAE, including death, at any time after the subject has been discharged from the study, the investigator must promptly notify the sponsor to comply with postmarketing reporting requirements for marketed products being used for approved indications.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and submitting SAE reports are provided in Section 10.3.

8.2.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

At each visit, subjects will be queried regarding any AEs that have occurred since the last visit. Subjects will be asked to volunteer information concerning AEs with a nonleading question such as, "How do you feel?" Study site personnel will then record all pertinent information. The study drug compliance record should also be reviewed to detect potential intentional or unintentional overdoses.

8.2.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and nonserious AEs will be followed to resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up. Further information on follow-up procedures is provided in Section 10.3.

8.2.4. Secondary Exposure to Testim and Fortesta

The FDA has mandated that secondary exposure data be collected on anyone exposed to Testim and Fortesta.

Investigators should explain to all subjects that there is the potential to transfer testosterone to another individual when vigorous skin-to-skin contact is made with the application site. Investigators should ask every subject about any possible secondary exposure of other

individuals due to the potential transfer. All such known secondary exposure must be reported to the sponsor within 24-hours on the Endo Serious Adverse Event (SAE)/Reportable Event form. AEs/SAEs that occur due to potential secondary exposure must be processed within the same SAE reporting timelines as those described in Section 10.3.

8.2.5. Pregnancy

All pregnancies that occur in the partner of a treated participant that are identified during or after this study, where the estimated date of conception is determined to have occurred during study treatment or within 28 days of the last study treatment need to be reported, followed to conclusion, and the outcome reported, even if the participant is discontinued from the study. The investigator should report (as outlined above) all pregnancies within 24 hours using the Pregnancy Form. Monitoring of the pregnancy should continue until conclusion of the pregnancy and follow-up information detailing the progress and outcome should be submitted on 1 or more Pregnancy Form(s) detailing progress, and a Two-Month Follow-up Pregnancy Report Form detailing the status of the infant should be submitted.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects, or any other serious events) must additionally be reported as such using the Serious Adverse Event (SAE)/Reportable Event Form (see Section 10.3). Spontaneous miscarriages should also be reported and handled as SAEs.

8.3. Treatment Overdose

Study treatment overdose is any accidental or intentional use of treatment in an amount higher than the dose indicated by the protocol for that subject. Study treatment compliance should be reviewed to detect potential instances of overdose (intentional or accidental).

Any treatment overdose during the study should be noted on the study drug eCRF.

An overdose is not an AE per se, however all AEs associated with an overdose should both be entered on the Adverse Event eCRF and reported using the procedures detailed in Section 10.3, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the Endo Serious Adverse Event (SAE)/Reportable Event Form and in an expedited manner, but should be noted as nonserious on the form and the Adverse Event eCRF.

8.3.1. Treatment Abuse/Misuse

Not applicable.

8.4. Pharmacokinetics

Not applicable.

8.5. Pharmacodynamics

Not applicable.

8.6. Genetics

Not applicable.

8.7. Biomarkers

Not applicable.

8.8. Medical Resource Utilization and Health Economics

Not applicable.

9. STATISTICAL CONSIDERATIONS AND METHODS

This section provides a general summary of the statistical methods to be used in analyzing study data. A more detailed statistical analysis plan (SAP) will be developed and finalized prior to the database lock.

9.1. Sample Size Determination

The objective of this study is to determine whether the study drugs have a clinically meaningful effect on ambulatory BP in hypogonadal men. The primary endpoint will be the mean change from baseline to EoS in 24-hour average SBP.

A sample size of 144 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 BP at EoS from baseline using 2-sided 95% CI with paired *t* test. The SD of 11 mm Hg is assumed.

It is assumed that 30% of enrolled subjects will be excluded from the Full Analysis Set (ie, subjects who discontinue early from the study, non-valid ABPM measures at baseline or EoS, etc), therefore a sample size of 206 for each of the 3 treatment groups is required.

9.2. Analysis Populations

Four analysis populations will be considered in the study: the Safety Population, the Intent-to-Treat Population (ITT), the Full Analysis Set (FAS), and the ABPM Population.

- Safety Population: will include all subjects who receive at least 1 dose/injection of study treatment. All safety analyses will be based on the Safety Population.
- Intent-to-Treat Population (ITT): will include all randomized subjects who have at least 1 dose/injection of study medication. Sensitivity analysis for primary and secondary efficacy analysis will be based on this population to assess the effect due to study discontinuation.
- Full Analysis Set (FAS): will include all ITT subjects with valid baseline and EoS ABPM assessments. All primary and secondary efficacy analysis will be based on the ABPM Population.

- ABPM Population: will include all FAS subjects with at least 85% compliance to treatment during the study. All primary and secondary efficacy analysis will be based on the ABPM Population.

9.3. Statistical Analyses

9.3.1. Efficacy Analysis

9.3.1.1. Primary Analysis

The primary endpoint will be the mean change from baseline to EoS in 24-hour average systolic ambulatory BP for each treatment group. This endpoint will be analyzed using an analysis of covariance (ANCOVA) model with baseline and study center, or pooled centers (if applicable), included as covariates. The mean estimate, and the corresponding 95% 2-sided confidence intervals (CIs) of the estimate, will be provided for each treatment group. If the upper limit of the 2-sided 95% CI falls below 3.0 mm Hg, it will be concluded that the tested treatment does not have statistical significance in increasing of 24-hour systolic ambulatory BP.

The mean of hourly systolic ambulatory BP at baseline and EoS will be graphically presented for each treatment group. The cumulative distribution function plots will also be plotted for the means of the daytime, nighttime, and 24-hour systolic ambulatory BP at baseline and EoS.

Descriptive analysis for the changes from baseline at each time point and 24-hour average for all ABPM parameters will be presented for each treatment group.

The ABPM Population across treatment groups will be further divided into the following 3 groups: subjects without hypertension, with hypertension untreated, and with hypertension treated. In addition, subgroups such as African Americans and the elderly will be examined. A similar analysis described in the primary analysis will be applied to these subgroups.

The descriptive statistics, ie, the number and percentage of subjects meeting the following BP thresholds will be provided: ≥ 160 mm Hg SBP, ≥ 100 mm Hg DBP, ≥ 20 mm Hg increase from baseline SBP and ≥ 15 mm Hg increase from baseline DBP.

9.3.1.2. Secondary Analysis

All secondary analysis will be summarized by treatment group using appropriate descriptive statistics.

9.3.1.3. Sensitivity Analysis

Two type of sensitivity analysis will be performed: 1) primary and secondary analysis based on ABPM population, 2) primary and secondary analysis based on ITT population to account for missing data due to study discontinuation.

9.3.2. Safety Analyses

Assessment of safety will be based on the incidence of AEs, AEs resulting in discontinuation, SAEs, laboratory parameters and vital signs. AE summaries will be provided showing the number and percentage of subjects who experienced at least 1 AE. Laboratory data and their change from baseline will be summarized using descriptive statistics. Shift tables to summarize

change from baseline to post baseline visits will also be presented (eg, normal to high, normal to low). Vital signs data and any changes from baseline will be summarized using descriptive statistics.

9.3.2.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by preferred term within system organ class. The number of AEs and the number of subjects reporting AEs will be listed and summarized descriptively by body system, preferred term, severity, and causality for each treatment group. Only treatment-emergent adverse events (TEAEs) (events that are new in onset or aggravated in severity following treatment) will be included in all summaries. SAEs (including death) will be summarized.

9.3.3. Serum Laboratory Testing

Serum testosterone levels will be summarized by treatment group and time point using appropriate descriptive statistics. For more information see the SAP.

9.4. Interim Analysis

Not applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This clinical study is designed to comply with the ICH Guidance on General Considerations for Clinical Trials (62 FR 6611, December 17, 1997), Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (62 FR 62922, November 25, 1997), Good Clinical Practice: Consolidated Guidance (62 FR 25692, May 9, 1997) and 21 CFR parts 50, 54, 56 and 312.

The study will be conducted in full compliance with ICH E6, the FDA guidelines for good clinical practice (GCP) and in accordance with the ethical principles that have their origins in the Declaration of Helsinki defined in 21 CFR, 312.120.

Approval by the IRB/IEC prior to the start of the study will be the responsibility of the investigator. A copy of approval documentation will be supplied to Endo along with a roster of IRB/IEC members that demonstrates appropriate composition or other documentation of assurance of appropriate composition per local and national regulations (eg, a Department of Health and Human Services Assurance Number will satisfy this requirement for IRBs in the United States).

The study protocol, the ICF, advertisements, materials being provided to subjects, and amendments (if any) will be approved to IRB/IECs at each study center in conformance with ICH E6, CFR Title 21 Part 56, and any other applicable local laws. The investigator is responsible for supplying the IRB/IEC with a copy of the current Investigator's Brochure, Package Insert, or Summary of Product Characteristics, as well as any updates issued during the study. During the course of the study, the investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB/IEC of SAEs or other significant safety findings, per the policy of the IRB/IEC. At the conclusion of the study, the investigator will submit a final report or close out report to the IRB/IEC and provide a copy to Endo.

Any amendment to this protocol will be provided to the investigator in writing by Endo. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB/IEC and the signature page, signed by the investigator, has been received by Endo. Where the protocol is amended to eliminate or reduce the risk to the subject, the amendment may be implemented before IRB/IEC review and approval. However, the IRB/IEC must be informed in writing of such an amendment and approval obtained within reasonable time limits. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the subject, and must be immediately reported to Endo.

The investigator will be responsible for supplying updated safety and/or study information to study subjects as it becomes available.

10.1.2. Financial Disclosure

The investigator and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The investigator is responsible for providing information on financial interests during the course of the study and for 1 year after the completion of the study.

10.1.3. Informed Consent Process

The ICF must be approved by the sponsor and the IRB/IEC before any subject provides consent. The investigator will provide the sponsor with a copy of the IRB/IEC-approved ICF and a copy of the IRB/IEC's written approval before the start of the study.

The ICF must contain all applicable elements of informed consent and the mandatory statements as defined by national and local regulations, including confidentiality.

If appropriate, the ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

At the Screening Visit (and at other time as may be required by the study or when changes are made to the consent form), subjects will read the consent form(s) and any privacy authorization as required by local and national regulations (such as the Health Insurance Portability and Accountability Act [HIPAA] authorization form), after being given an explanation of the study. Before signing the consent form(s) and the privacy authorization form (if applicable), subjects will have an opportunity to ask questions about the study and discuss the contents of these forms with study site personnel. The consent/assent process shall be recorded in source documents.

Subjects must assent understanding of and voluntarily sign these forms in compliance with ICH GCP and all applicable national and international regulations, before participating in any study-related procedures. Subjects will be made aware that they may withdraw from the study at any time for any reason.

All versions of each subject's signed ICF must be kept on file by the site for possible inspection by regulatory authorities and the sponsor. Signed copies of the consent form(s) and the privacy authorization form, if applicable, will be given to the subject.

The subjects will be made aware of their right to see and copy their records related to the study for as long as the investigator has possession of this information. If the subject withdraws consent and/or HIPAA authorization, the investigator can no longer disclose health information, unless it is needed to preserve the scientific integrity of the study.

10.1.4. Data Protection

Study subjects will be assigned a unique identifier by the sponsor or designee. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure (in accordance with local and/or national law) must also be explained to the subject.

The subject must be informed that his medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committee Structure

No monitoring committees will be used for this study.

10.1.6. Dissemination of Clinical Study Data

Aggregate results data will be provided to the sites that actively enrolled subjects into this study after the clinical study report is finalized.

Study results and de-identified individual subject data will be released as required by local and/or national regulation.

10.1.7. Data Quality Assurance

Steps to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigators and associated personnel prior to start of the study, and periodic monitoring visits conducted by the sponsor or sponsor representative. Significant and/or repeated noncompliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in investigator site termination and regulatory authority notification.

The sponsor or its designee will utilize qualified monitors to review and evaluate activities conducted at investigator sites.

The data will be entered into the clinical study database in a timely fashion and will be verified for accuracy, following procedures defined by the sponsor (or designee). Data will be processed and analyzed following procedures defined by the sponsor (or designee).

The study will be monitored and/or audited at intervals to ensure that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the study protocol, ICH E6 consolidated guidelines, and other applicable regulations. The extent, nature, and frequency of monitoring and/or audits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. At the conclusion of a program, a compliance statement will be generated by the sponsor (or designee) listing all audit activities performed during the clinical study.

All data recordings and source documentation (including electronic health records) must be made available to the sponsor (or designee), FDA and any other regulatory agencies that request access to study records for inspection and copying, in keeping with national and local regulations.

The investigator shall permit audits and inspections by the sponsor, its representatives, and members of regulatory agencies. The investigator should immediately notify the sponsor of an upcoming FDA or other regulatory agency inspection.

10.1.8. Source Documents

All subject information recorded in the eCRF will be attributable to source data from the investigational site unless otherwise outlined in this protocol.

Source documents include but are not limited to original documents, data, and records such as hospital/medical records (including electronic health records), clinic charts, lab results, subject diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. At a minimum, all data required to be collected by the protocol should have supporting source documentation for entries in the eCRF, unless the protocol specifies that data can be recorded directly on/in the eCRF or other device.

The investigator shall retain and preserve 1 copy of all data collected or databases generated in the course of the study, specifically including but not limited to those defined by GCP as essential. Essential documents should be retained until at least 3 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational medicinal product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. Prior to destruction of any study essential documents, the investigator must first obtain written approval from the sponsor.

10.1.9. Study and Site Closure

The sponsor has the right to suspend or terminate the study at any time. The study may be suspended or terminated for any reason.

10.1.10. Publication Policy

All data generated in this study are the property of Endo. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the investigator will be subject to mutual agreement between the investigator and Endo.

10.2. Appendix 2: Clinical Laboratory Tests

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.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definitions

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 preexisting condition associated temporally with the use of the study medication whether or not considered related to the study medication. AEs will be captured once a subject has signed the informed consent. AEs include:

- Changes in the general condition of the subject.
- Subjective symptoms offered by or elicited from the subject.
- Objective signs observed by the investigator or other study personnel.
- All concurrent diseases that occur after the start of the study, including any change in severity or frequency of preexisting disease.
- All clinically relevant laboratory abnormalities or physical findings that occur during the study.

A TEAE is any condition that was not present prior to treatment with study medication but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated).

An SAE is defined as an AE that:

- Results in death.
- Is immediately life-threatening (there is an immediate risk of death from the AE as it occurred; this does not include an AE that had it occurred in a more serious form may have caused death).
- Results in or prolongs an inpatient hospitalization (Note: a hospitalization for elective or preplanned surgery, procedure, or drug therapy does not constitute an SAE).
- Results in permanent or substantial disability (permanent or substantial disruption of one's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect (in offspring of a subject using the study medication regardless of time to diagnosis).
- Is considered an important medical event.

Important medical events are defined as events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the other serious outcomes. Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.3.2. Relationship to Study Drug

The degree of "relatedness" of the AE to the study medication must be described using the following scale:

- **Not related** indicates that the AE is definitely not related to the study medication.
- **Unlikely related** indicates that there are other, more likely causes and study medication is not suspected as a cause.
- **Possibly related** indicates that a direct cause and effect relationship between study medication and the AE has not been demonstrated, but there is evidence to suggest there is a reasonable possibility that the event was caused by the study medication.
- **Probably related** indicates that there is evidence suggesting a direct cause and effect relationship between the AE and the study medication.

It is the sponsor's policy to consider "probably related" and "possibly related" causality assessments as positive causality. "Not related" and "unlikely related" causality assessments are considered as negative causality.

Assessments will be recorded on the eCRF and must indicate clearly the relationship being assessed. For example, an AE that appears during a placebo run-in phase would be assessed with respect to the placebo treatment received and/or study procedures conducted during this phase. If the AE continued into an active treatment phase, the relationship would be assessed for the active treatment phase only if the AE worsened.

10.3.3. Intensity Assessment

The intensity (or severity) of AEs is characterized as mild, moderate, or severe:

- **Mild** AEs are usually transient, requiring no special treatment, and do not interfere with the subject's daily activities.
- **Moderate** AEs introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- **Severe** AEs interrupt a subject's usual daily activity and typically require systemic drug therapy or other treatment.

10.3.4. Reporting Adverse Events and Serious Adverse Events

10.3.4.1. Reporting Adverse Events

Throughout the study, AEs will be documented on the source document and on the appropriate page of the eCRF whether or not considered treatment-related. This includes any new signs, symptoms, injury, or illness, including increased severity of previously existing signs, symptoms, injury, or illness. Conditions existing prior to screening will be recorded as part of the subject's medical history. The investigator is responsible for assessing the relationship of AEs to the study medication; relationship will be classified as not related, unlikely related, possibly related, or probably related.

All AEs will be collected by the investigator from the time of signing the ICF through the Day 115 EoS Visit (Testim and Fortesta) and Day 108 (Aveed); or for 28 days after the last dose of study treatment in those subjects who terminate early. All ongoing AEs must be followed until resolution or for 28 days after the last dose of study treatment, whichever comes first.

10.3.4.2. Reporting Serious Adverse Events

Any SAE, including death resulting from any cause, which occurs to any subject participating in this study must be reported via email or fax by the investigator using the Endo Serious Adverse Event (SAE)/Reportable Event Form within 24 hours of first becoming aware of the SAE. SAEs will be collected by the investigator from the time of signing the ICF through the Day 115 EoS visit (Testim and Fortesta) and Day 108 (Aveed); or for 28 days after the last dose of study medication in those subjects who terminate early. SAEs that occur within 28 days, following cessation of the study treatment, or within 28 days, following premature discontinuation from the study for any reason, must also be reported within the same timeframe. If the investigator learns of any SAE, including death, at any time after the subject has been discharged from the study, the investigator must promptly notify the sponsor to comply with postmarketing reporting requirements for marketed products being used for approved indications. Follow-up information collected for any initial report of an SAE must also be reported to the sponsor within 24 hours of receipt by the investigator.

All SAEs will be followed until resolution, stabilization of condition, or until follow-up is no longer possible.

All SAEs should be reported via email (safety@endo.com) or fax (610-968-7135).

The sponsor will determine whether the SAE must be reported within 7 or 15 days to regulatory authorities in compliance with local and regional law. If so, the sponsor (or the sponsor's representative) will report the event to the appropriate regulatory authorities. The investigator will report SAEs to the IRB/IEC per their IRB/IEC policy.

10.3.4.3. Follow-up Procedures for Serious Adverse Events

To fully understand the nature of any SAE, obtaining follow-up information is important. Whenever possible, relevant medical records such as discharge summaries, medical consultations, and the like should be obtained. In the event of death, regardless of cause, all attempts should be made to obtain the death certificate and any autopsy report. These records should be reviewed in detail, and the investigator should comment on any event, lab abnormality, or any other finding, noting whether it should be considered a serious or non-serious AE, or whether it should be considered as part of the subject's history. In addition, all events or other findings determined to be SAEs should be identified on the Endo Serious Adverse Event (SAE)/ Reportable Event Form and the investigator should consider whether the event is related or not related to study drug. All events determined to be nonserious should be reported on the eCRF.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

See Section 5.

10.5. Appendix 5: Genetics

Not applicable.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Not applicable.

10.7. Appendix 7: Medical Device Incidents

Not applicable.

10.8. Appendix 8: Country-specific Requirements

Not applicable.

11. INVESTIGATOR'S STATEMENT

I agree to conduct the study in accordance with the protocol, and with all applicable government regulations and Good Clinical Practice guidance.

_____ _____/_____/_____

Investigator's Signature Date

_____

Typed Name of Investigator

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