Title Page

Protocol Title: A Phase IV, Multi-center, Open-label, Single-arm 24-hour Ambulatory Blood Pressure Monitoring (ABPM) Study of 16 Weeks Treatment with Androderm® in Hypogonadal Men

Protocol Number: 3146-402-016

Product: Androderm® (testosterone transdermal system)

Brief Protocol Title: Androderm® ABPM Study in Hypogonadal Men

Study Phase: IV

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase IV, Multi-center, Open-label, Single-arm, 24-hour Ambulatory Blood Pressure Monitoring (ABPM) Study of 16 Weeks Treatment with Androderm® in Hypogonadal Men

Protocol Number: 3146-402-016

Brief Title: Androderm® (testosterone transdermal system)

Study Rationale:

Prior clinical studies of Androderm collected and evaluated pre- and post-treatment systolic and diastolic blood pressure (BP) by cuff measurements. No significant trends in cuff BP values were noted in patients treated with Androderm.

The Food and Drug Administration (FDA) has issued a postapproval requirement because it is not fully known whether any changes in BP, when assessed using 24-hour ABPM, will occur with a transdermal formulation of testosterone, such as Androderm. Intensive 24-hour ABPM monitoring will allow for a more definitive exclusion of a clinically meaningful effect of Androderm on BP. Twenty-four-hour ABPM provides a much larger number of readings throughout the day and night, providing more reproducible mean 24-hour, daytime, and night-time values.

Therefore, this Phase IV, multi-center, open-label, single-arm study aims to evaluate the effect of once daily Androderm on BP parameters as measured by 24-hour ABPM in hypogonadal men after 16 weeks of treatment.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To determine whether Androderm has a meaningful effect on 24-hour average systolic blood pressure (SBP) as measured by ABPM in men who use testosterone replacement treatment	• Change from baseline in 24-hour average SBP obtained at Week 16
Secondary	
• To determine whether Androderm has a meaningful effect on 24-hour blood pressure (BP) parameters as measured by ABPM in men who use testosterone replacement treatment	• Change from baseline in 24-hour average diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse pressure and heart rate obtained at Week 16
Exploratory	
• To determine whether Androderm has a meaningful effect on BP parameters as measured by ABPM in men who use testosterone replacement treatment	• Change from baseline in daytime average SBP, DBP, MAP, pulse pressure and heart rate obtained at Week 16 • Change from baseline in night-time average SBP, DBP, MAP, pulse pressure and heart rate obtained at Week 16 • Change from baseline over time (hourly average) by nominal clock time and time after dose: SBP, DBP, MAP, pulse pressure and heart rate • Status (yes/no) of participants with new anti-hypertensive medications • Status (yes/no) of participants with dose increases in anti-hypertensive medications • Outlier responder for participants meeting SBP ≥ 160 mm Hg for 24-hour average • Outlier responder for participants meeting SBP change from baseline ≥ 20 mm Hg for 24-hour average • Outlier responder for participants meeting DBP ≥ 100 mm Hg for 24-hour average • Outlier responder for participants meeting DBP change from baseline ≥ 15 mm Hg for 24-hour average • Status (yes/no) of participants with normalized testosterone concentrations at Week 16
Safety • To demonstrate the safety of once daily Androderm for 16 weeks in hypogonadal men	**Safety Parameters** • Adverse events (AEs), clinical laboratory values, vital signs, and physical examination

Overall Study Design:

This is a multi-center, open-label, single-arm study in hypogonadal men to evaluate the effect of once daily Androderm on BP parameters as measured by 24-hour ABPM.

Number of Participants:

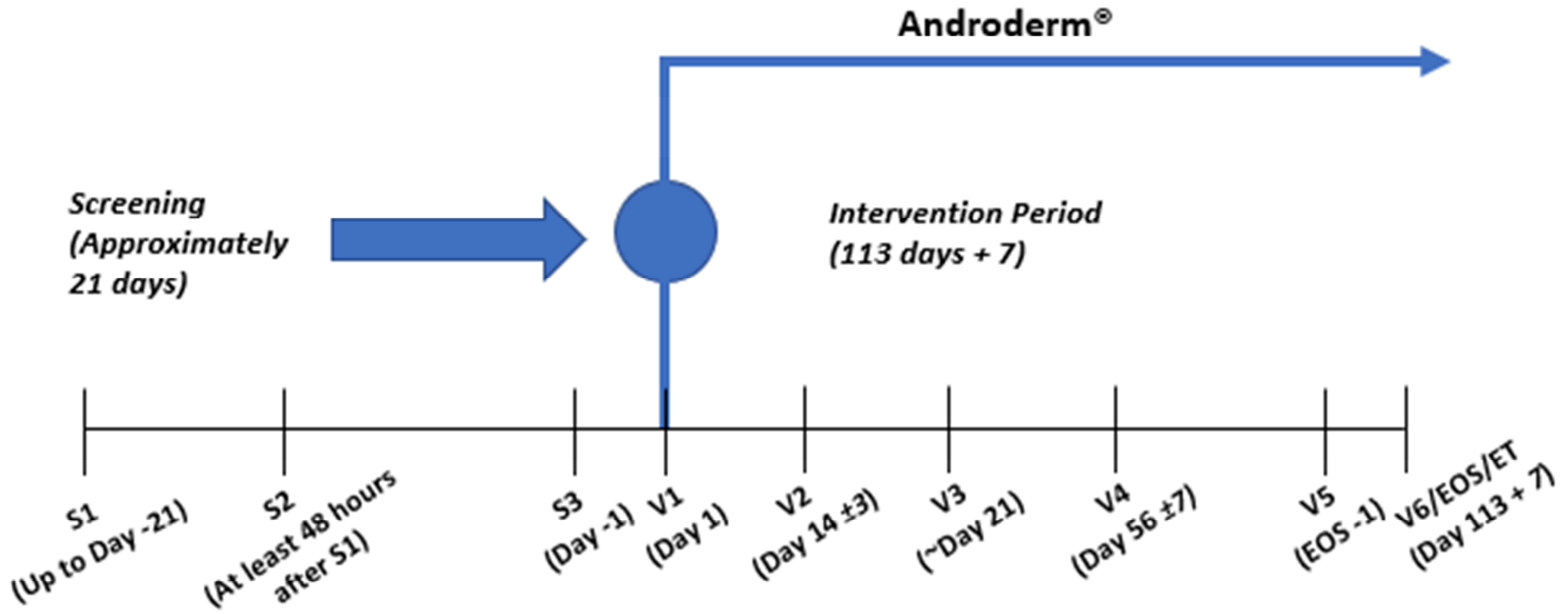
Approximately 300 participants will be screened, to achieve 150 enrolled who receive ≥ 1 administration of study intervention, and 120 participants with interpretable 24-hour ABPM data at both baseline and the end of Week 16. Participants who prematurely discontinue from the study will not be replaced but will be followed to obtain the last 24-hour ABPM assessment.

Intervention Groups and Study Duration:

The study will consist of a screening period of approximately 3 weeks (21 days), followed by an intervention period of 16 weeks (minimum of 113 + 7 days), for a total study duration of approximately 19 weeks (133 days). All participants who meet the criteria for participation in the study will be administered Androderm at the starting dose of 4 mg/day. On Visit 2, study participants will have morning serum concentrations of testosterone measured. If participants have a serum concentration below 400 ng/dL, the dose of Androderm will be increased to 6 mg/day (one 4 mg/day system and one 2 mg/day system). If the serum concentration is above 930 ng/dL, the dose of Androderm will be decreased to 2 mg/day. All others will remain on 4 mg/day.

Data Monitoring Committee: No

1.2. Schema


Androderm®
Screening
(Approximately
21 days)
Intervention Period
(113 days + 7)
S1
(Up to Day -21)
S2
(At least 48 hours
after S1)
S3
(Day -1)
V1
(Day 1)
V2
(Day 14 ±3)
V3
(~Day 21)
V4
(Day 56 ±7)
V5
(EOS -1)
V6/EOS/ET
(Day 113 + 7)

1.3. Schedule of Activities (SoA)

Study procedures are recommended to be done in sequence as listed in the below schedule, but the sequence is not mandatory.

Table 1-1 Schedule of Activities

Procedure	Screening Period			Intervention Period/Study Day						Notes
Visit Name	S1	S2	S3	V1	V2	V3/TC	V4	V5	V6/EOS /ET	V3 only if dose titration is needed, otherwise TC
Visit Windows	Up to Day -21	At least 48 hours after S1	Day -3 to -1	Day 1	Day 14 ± 3	~Day 21	Day 56 ± 3	EOS -1	Day 113 + 7	V3/TC after V2 morning testosterone results are available
Informed consent	X									
Inclusion and exclusion criteria	X	X	X	X						Recheck eligibility at V1 before dispensing study intervention
Demography	X									
Medical and surgical history (includes prior medications)	X									
Height and weight	X								X	Height at S1 only
Vital signs	X	X	X	X	X		X	X	X	Triplicate sitting BP and heart rate; temperature Vital signs to be taken before blood collection
Physical examination		X		X					X	
Fasting morning testosterone	X	X			X					Between 0700 and 1100 local time

Procedure	Screening Period			Intervention Period/Study Day						Notes
Visit Name	S1	S2	S3	V1	V2	V3/TC	V4	V5	V6/EOS /ET	V3 only if dose titration is needed, otherwise TC
Visit Windows	Up to Day -21	At least 48 hours after S1	Day -3 to -1	Day 1	Day 14 ± 3	~Day 21	Day 56 ± 3	EOS -1	Day 113 + 7	V3/TC after V2 morning testosterone results are available
PK total testosterone assessment			X		X		X	X		Obtain testosterone sample before ABPM device placement at S3 and V5 At V2 and V4, obtain testosterone sample between 0700 and 1100 local time The time of sample collection and ABPM device placement should be noted
Fasting laboratory assessments	X								X	Hematology (including PT and INR), chemistry (including liver chemistry and HbA1c), PSA, urinalysis
I-PSS		X							X	
Prostate digital rectal exam		X							X	Not required if normal digital rectal exam within 6 months of S1; at V6/EOS/ET only if clinically indicated
Apply ABPM			X					X		24-hour ABPM at ET if feasible
Remove ABPM				X					X	24 hours after applying ABPM device
Dispense/Begin study intervention				X		X				At V3 only if dose titration is needed

Procedure	Screening Period			Intervention Period/Study Day						Notes
Visit Name	S1	S2	S3	V1	V2	V3/TC	V4	V5	V6/EOS /ET	V3 only if dose titration is needed, otherwise TC
Visit Windows	Up to Day -21	At least 48 hours after S1	Day -3 to -1	Day 1	Day 14 ± 3	~Day 21	Day 56 ± 3	EOS -1	Day 113 + 7	V3/TC after V2 morning testosterone results are available
Return/Reconcile study intervention						X			X	At V3 only if dose titration is needed
AE review	←==========								→	
SAE review	←==========								→	
Concomitant medication review				←==========					→	

2. Introduction

Endogenous androgens, which include testosterone and dihydrotestosterone, are required for the growth and development of male sex organs, other various organs, and for the maintenance of secondary sex characteristics. Testosterone is a steroid hormone that exerts its physiologic effect throughout a man's life. Testosterone exerts its development of secondary sex characteristics in men during puberty, in which men begin to observe growth and maturation of the prostate, penis, scrotum, etc. (Ullah 2014).

Hypogonadism is a condition that results from insufficient physiological concentrations of serum testosterone produced by the testes and/or an abnormal number of spermatozoa present. Hypogonadism is split into primary and secondary hypogonadism. Primary hypogonadism occurs when there are abnormalities in the testes, whereas secondary hypogonadism is seen when there are defects in the hypothalamus or the pituitary. Signs and symptoms associated with hypogonadism include delayed sexual development, loss of body hair, reduced libido, erectile dysfunction, fatigue, mood depression, and osteoporosis (Bhasin 2018).

Testosterone replacement therapy has been used to maintain secondary sex characteristics and to halt symptoms of testosterone deficiency (Bhasin 2018). Androderm® (testosterone transdermal system) is an androgen indicated for replacement therapy in adult men with conditions associated with a deficiency or absence of endogenous testosterone. Through its self-contained transdermal system, Androderm provides a continuous daily dose of testosterone, delivering physiologic concentrations of testosterone, resulting in circulating testosterone levels that are approximately equal to the normal concentration range seen in healthy adult men (300 to 1030 ng/dL). Androderm has been available since 29 September 1995 and is recognized as a replacement therapy in males for the indications of primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired) (Allergan 2018).

2.1. Study Rationale

Prior clinical studies of Androderm collected and evaluated pre- and post-treatment systolic and diastolic BP by cuff measurements. No significant trends in cuff BP values were noted in patients treated with Androderm.

The FDA has issued a postapproval requirement because it is not fully known whether any changes in BP, when assessed using 24-hour ABPM, will occur with a transdermal formulation of testosterone, such as Androderm. Intensive 24-hour ABPM monitoring will allow for a more definitive exclusion of a clinically meaningful effect of Androderm on BP. Twenty-four-hour ABPM provides a much larger number of readings throughout the day and night, providing more reproducible mean 24-hour, daytime, and night-time values. It more accurately identifies white-coat hypertension, where clinic BP measurements are high but ABPM readings are normal, and masked hypertension, where clinic BP measurements are low but ABPM readings are high (Parati 2014).

Unlike cuff BP measurements, studies with ABPM evaluating hypertensive patients have shown a paucity, or even a lack, of a placebo effect (Dupont 1987, Mutti 1991, Mancia 1995). Dupont et al demonstrated that placebo significantly decreased in-clinic systolic and diastolic BP when measured by cuff measurements after 4 weeks ($p < 0.001$) but did not significantly decrease systolic and diastolic BP when measured by ABPM. Similarly, Mutti et al demonstrated that, following 4 weeks of placebo, in-clinic systolic and diastolic BP was significantly reduced (-9.6 ± 2.6 and -3.1 ± 1.7 mm Hg, $p < 0.01$, respectively), while 24-hour ABPM did not show any significant change. Finally, Mancia et al again demonstrated that administration of placebo significantly decreased systolic and diastolic BP measured in the clinic (-5.3 ± 1.1 and -4.4 ± 0.6 mm Hg, $p < 0.01$, respectively), while no significant reductions were noted with 24-hour ABPM. These studies show that an open-label single-arm study design is adequate if 24-hour ABPM is being used to assess effects on BP.

Therefore, this Phase IV, multi-center, open-label, single-arm study aims to evaluate the effect of once daily Androderm on BP parameters as measured by 24-hour ABPM in hypogonadal men after 16 weeks of treatment.

2.2. Background

Currently, there are several FDA-approved and commercially available options for the treatment of hypogonadism. Per the 2018 Endocrine Society Clinical Practice Guidelines, testosterone replacement therapy continues to be the mainstay of therapy for the treatment of primary hypogonadism and hypogonadotropic hypogonadism. Although testosterone therapy remains a first-line treatment option for the treatment of hypogonadism, the effect it has on BP parameters is not fully understood.

2.3. Benefit/Risk Assessment

Patients with either primary hypogonadism (congenital or acquired) or hypogonadotropic hypogonadism (congenital or acquired), characterized by baseline morning testosterone < 300 ng/dL, may experience symptoms that include, but are not limited to, erectile dysfunction, osteoporosis, fatigue, decreased libido, hot flashes, etc.

In several clinical trials of males between 15 and 76 years old, participants with male hypogonadism were treated with 2 mg/day to 5 mg/day of Androderm for up to 28 days. Androderm produced average morning serum testosterone concentrations within the normal reference range in 92% to 97% of participants (Allergan 2018).

The most common adverse reactions reported in clinical trials were application site reactions in 28% to 48% of participants. Other less common adverse reactions are prostate abnormalities, headache, and depression (reported in 5%, 4%, and 3% of participants in clinical studies). Adverse reactions reported by < 3% of participants included: chills, diarrhea, rash, fatigue, gastrointestinal bleeding, gastroesophageal reflux disease, hemarthrosis, hematuria, polyuria, prostatitis, body pain, pelvic pain, hypertension, peripheral vascular disease, increased appetite, accelerated growth, anxiety, confusion, decreased libido, impotence, paresthesia, thinking

abnormalities, vertigo, acne, dysuria, urinary incontinence, urinary tract infection, testicular abnormalities, and prostate carcinoma.

From postmarketing experience, AEs of myocardial infarction, stroke and venous thromboembolism have been reported, though because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of Androderm may be found in the US Package Insert.

Overall, based on the safety profile of the product, the benefit-risk of Androderm remains positive when used for approved indications.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine whether Androderm has a meaningful effect on 24-hour average SBP as measured by ABPM in men who use testosterone replacement treatment	• Change from baseline in 24-hour average SBP obtained at Week 16
Secondary	
• To determine whether Androderm has a meaningful effect on 24-hour BP parameters as measured by ABPM in men who use testosterone replacement treatment	• Change from baseline in 24-hour average DBP, MAP, pulse pressure and heart rate obtained at Week 16
Exploratory	
• To determine whether Androderm has a meaningful effect on BP parameters as measured by ABPM in men who use testosterone replacement treatment	• Change from baseline in daytime average SBP, DBP, MAP, pulse pressure and heart rate obtained at Week 16 • Change from baseline in night-time average SBP, DBP, MAP, pulse pressure and heart rate obtained at Week 16 • Change from baseline over time (hourly average) by nominal clock time and time after dose: SBP, DBP, MAP, pulse pressure and heart rate • Status (yes/no) of participants with new anti-hypertensive medications • Status (yes/no) of participants with dose increases in anti-hypertensive medications • Outlier responder for participants meeting SBP ≥ 160 mm Hg for 24-hour average • Outlier responder for participants meeting SBP change from baseline ≥ 20 mm Hg for 24-hour average • Outlier responder for participants meeting DBP ≥ 100 mm Hg for 24-hour average • Outlier responder for participants meeting DBP change from baseline ≥ 15 mm Hg for 24-hour average • Status (yes/no) of participants with normalized testosterone concentrations at Week 16
Safety • To demonstrate the safety of once daily Androderm for 16 weeks in hypogonadal men	**Safety Parameters** • Adverse events (AEs), clinical laboratory values, vital signs, and physical examination

4. Study Design

4.1. Overall Design

This is a multi-center, open-label, single-arm study in hypogonadal men to evaluate the effect of once daily Androderm on BP parameters as measured by 24-hour ABPM. It is projected that approximately 40 sites in the United States will enroll approximately 150 participants who will receive at least 1 dose for this study.

The study will consist of a screening period of approximately 3 weeks (21 days), followed by an intervention period of 16 weeks (minimum of 113 + 7 days), for a total study duration of approximately 19 weeks (133 days). All participants who meet the criteria for participation in the study will be administered Androderm at the starting dose of 4 mg/day. On Visit 2, study participants will have morning serum concentrations of testosterone measured. If participants have a serum concentration below 400 ng/dL, the dose of Androderm will be increased to 6 mg/day (one 4 mg/day system and one 2 mg/day system). If the serum concentration is above 930 ng/dL, the dose of Androderm will be decreased to 2 mg/day. All others will remain on 4 mg/day.

Approximately 300 participants will be screened to achieve approximately 150 enrolled participants who will receive at least 1 dose and 120 participants with interpretable 24-hour ABPM data at both baseline and the end of Week 16. Participants who prematurely discontinue from the study will not be replaced but will be followed to obtain the last 24-hour ABPM assessment.

4.2. Scientific Rationale for Study Design

A single-arm design is utilized as there are no appropriate active comparators for this study. While there are many approved formulations of testosterone, including transdermal, intramuscular, and intravenous ones, none are considered appropriate as parallel-controls due to lack of available ABPM data to estimate their effect on BP in hypogonadal men. Furthermore, unlike cuff BP measurements, past studies that have evaluated participants with hypertension have shown that there is a lack of a placebo effect with ABPM (Dupont 1987, Mutti 1991, Mancia 1995). ABPM more accurately identifies white-coat hypertension, where clinic BP measurements are high but ABPM readings are normal, and masked hypertension, where clinic BP measurements are low but ABPM readings are high (Parati 2014).

4.3. Justification for Dose

Androderm is approved by the FDA for replacement therapy of endogenous testosterone in males with primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired). The recommended starting dose for Androderm is one 4 mg/day system, applied nightly, every 24 hours. 2 mg/day and 4 mg/day Androderm

transdermal systems are FDA approved doses for the treatment of men with hypogonadism and will be used throughout this trial.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the schedule of activities for the last participant in the study. A participant is considered to have completed the study if he has not been terminated early and has completed all phases of the study including Visit 6 (Day 113 [+ 7 days]).

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1.	**Age**
1.01	Participant must be 18 to 80 years of age inclusive, at the time of signing the informed consent
2.	**Type of Participant and Disease Characteristics**
2.01	Two serum testosterone levels < 300 ng/dL in the morning, between 0700 and 1100 local participant's time, on 2 separate days, at least 48 hours apart
2.02	Naïve to testosterone replacement, clomiphene, compounded or over-the-counter androgenic steroid derivatives, and DHEA, including investigational products that may affect the reproductive hormonal system or has not been treated with these compounds in the past 6 months
3.	**Weight and Body Mass Index**
3.01	BMI < 35 kg/m^2
4.	**Sex**
4.01	Male
5.	**Contraceptives**
5.01	Male participants willing to minimize the risk of inducing pregnancy for the duration of the clinical study and follow-up period
	A male participant must agree to use contraception as detailed in Appendix 7 of this protocol during the intervention period and for at least 30 days after the last dose of study intervention and refrain from donating sperm during this period.

6.	**Informed Consent**
6.01	Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
6.02	Signed informed consent from the participant has been obtained prior to any study-related procedures.
6.03	Signed documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable (eg, Written Authorization for Use and Release of Health and Research Study Information)
7.	**Other**
7.01	Able, as assessed by the investigator, and willing to follow study instructions and likely to complete all required study visits

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1.	**Medical Conditions**
1.01	Uncontrolled systemic disease or clinically significant disease, in particular, liver, kidney or heart disease, including hypertension, congestive heart failure, coronary heart disease, chronic atrial fibrillation, sleep apnea or psychiatric illness, that in the investigator's opinion, would put the participant at an unacceptable risk with exposure to Androderm
1.02	History of prostate (current or in the past) or breast cancer
1.03	Had a recent (within 2 years) history of stroke, transient ischemic attack, acute coronary event, venous thrombotic, or thromboembolic event
1.04	History of alcohol or other substance abuse within the previous 2 years
1.05	Known allergy or sensitivity to the study intervention or its components or other testosterone replacement medications

2.	**Prior/Concomitant Therapy**
2.01	If receiving the following medications, doses must be stable (for at least 4 weeks) with no intention of changing during screening and for the duration of the study: • Medications for diabetes, hypertension, hyperlipidemia, or anticoagulation • Glucocorticoids > 7.5 mg prednisone equivalent per day (eg, hydrocortisone 30 mg, methylprednisolone 6 mg, or dexamethasone 1.2 mg)
2.02	Use of any over-the-counter or herbal preparations containing testosterone is prohibited within 7 days or 5 half-lives (whichever is longer) prior to screening and for the duration of the study
3.	**Prior/Concurrent Clinical Study Experience**
3.01	Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study
4.	**Diagnostic Assessments**
4.01	Mean triplicate sitting BP (by cuff) > 140/90 mm Hg during all screening visits
4.02	HbA1c > 8.5%
4.03	Abnormal prostate digital rectal examination (palpable nodules) within 6 months of screening
4.04	PSA > 3.0 ng/mL
4.05	Hematocrit > ULN
4.06	Prolactin > ULN
4.07	Severe lower urinary tract symptoms as indicated by an I-PSS > 19 at screening
4.08	Abnormal and clinically significant results according to the investigator or designee, on physical examination, medical history, hematology, clinical chemistry, or urinalysis
5.	**Other**
5.01	Participant who works night shifts or who will need to perform strenuous manual labor while wearing the ABPM monitor

5.02	Participant has a condition or is in a situation that, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study
5.03	Directly or indirectly involved in the conduct and administration of this study as an investigator, subinvestigator, study coordinator, or other study staff member; employee of the sponsor; first degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the study; or enrolled in the study by another clinical site

5.3. Lifestyle Considerations

No lifestyle considerations or restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes indicating screen failure as reason for ending the study, demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failures) may not be rescreened.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Table 6-1 Study Interventions

Study Intervention Name	Androderm® (testosterone transdermal system)
Dose Formulation	2 mg/day and 4 mg/day transdermal system
Route of Administration	Transdermal
Dosing Instructions	All participants will receive a starting dose of Androderm 4 mg/day applied nightly at approximately 2200. At Visit 2, a fasting morning testosterone concentration will be measured. A testosterone concentration < 400 ng/dL will require an increase in dose to 6 mg/day (one 4 mg/day system and one 2 mg/day system) applied nightly. A testosterone concentration > 930 ng/dL will require a decrease in dose to 2 mg/day applied nightly. Prior to ABPM sessions, the application site should not be on the arm used for the blood pressure cuff.
Packaging and Labeling	Study intervention will be provided in boxes. Each box will be labeled as required per country requirements.
Manufacturer	Allergan

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions will be provided by the sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label, single-arm study. No blinding of assigned study intervention will occur.

Each participant who provides informed consent will be assigned a participant ID number. Participant ID numbers will be unique 11-digit numbers that follow the participant throughout the study and consist of the 3-digit protocol number (402), 5-digit site number, and 3-digit screening number.

6.4. Study Intervention Compliance

For home dosing, study intervention compliance will be closely monitored by counting the number of systems dispensed and returned. Before dispensing new study intervention at each visit, study center personnel will make every effort to collect all unused study intervention.

The study staff will keep an accurate drug disposition record that specifies the amount of study intervention dispensed to each participant.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter, prescription medicines, vitamins, herbal supplements, and/or cannabis or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Indication
- Dates of administration including start and end dates
- Dosage information including dose and frequency

At screening, during the study, and at EOS, study staff will question each participant specifically on the use of concomitant medications. Study staff must notify the sponsor immediately if a participant consumes any concomitant medications not permitted by the protocol. Participants who admit to using prohibited concomitant medications may be discontinued from the study at the discretion of the investigator or the sponsor.

Concurrent chronic medications, such as medications for hypertension, hyperlipidemia, diabetes, and anticoagulation should be administered in dosages with no intention of changing for the duration of the study.

6.5.1. Prohibited Interventions and Washout Before the Study

Over the counter or herbal preparations containing testosterone are prohibited 7 days or 5 half-lives (whichever is longer) before screening and throughout the study.

The decision to administer a prohibited medication/intervention during the study period is done with the safety of the study participant as the primary consideration. When possible, the sponsor is to be notified before the prohibited medication/intervention is administered.

6.5.2. Permitted Interventions

Therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/intervention is in question, please contact the sponsor.

The sponsor or designee should be contacted if there are any questions regarding concomitant or prior therapy.

Any medication taken during the study between the date of the first dose of study intervention and the date of the EOS visit will be recorded in the eCRF as a concomitant medication; any medication started after the EOS visit will not be considered a concomitant medication and should not be captured in the eCRF.

6.5.3. Rescue Medicine

Rescue medicine is not applicable.

6.5.4. Prohibited Interventions During the Study

Participants must abstain from taking prescription or nonprescription drugs (including drugs containing testosterone, vitamins, and dietary or herbal supplements) within 7 days or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

6.6. Dose Modification

All participants will initially receive a standard starting dose of Androderm of 4 mg/day which will be applied nightly at approximately 2200, starting on Visit 1. At Visit 2, a fasting morning testosterone concentration will be measured. Visit 3 will occur when results of the fasting testosterone concentration are available. Participants with a testosterone concentration < 400 ng/dL will require an increase in dose to 6 mg/day (one 4 mg/day system and one 2 mg/day system) applied nightly. Participants with a testosterone concentration of > 930 ng/dL will require a decrease in dose to 2 mg/day (one 2 mg/day system) applied nightly. All others will remain on 4 mg/day.

If all doses of study intervention are well-tolerated, the total duration of participation in the study will be approximately 19 weeks (3 weeks for screening, plus 16 weeks [Day 1 through Visit 6/EOS] of intervention therapy).

6.7. Intervention after the End of the Study

No intervention will be given after the EOS.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

A premature discontinuation will occur if a participant who signs the ICF and receives study intervention ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

Notification of early participant discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented.

Reasons for discontinuation from the study treatment and/or the study may include the following commonly used or other acceptable terms:

Commonly Used Terms	Other Acceptable Terms
Adverse event	Death
Completed	Disease relapse
Lack of efficacy	Technical problems
Lost to follow-up	
Non-compliance with study drug	
Other	
Physician decision	
Protocol deviation	
Screen failure	
Site terminated by sponsor	
Study terminated by sponsor	
Withdrawal by subject	

7.1. Discontinuation of Study Intervention

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

If feasible, 24-hour ABPM should be collected at the time of intervention discontinuation.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he 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 participant fails to return for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record.
- Should the participant continue to be unreachable, he will be considered to have withdrawn from the study.
- Discontinuation of specific sites, or of the study as a whole, are handled as part of Appendix 1.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

8.1. Efficacy Assessments

8.1.1. ABPM Assessments

BP parameters, including SBP, DBP, MAP, pulse pressure, and heart rate will be collected by 24-hour ABPM according to the SoA. The ABPM device is a validated device, recommended by relevant, well-known international hypertension societies and is FDA approved. All ABPM measurements will be done using the same make and model ABPM device supplied by the central vendor, and for each participant, the same device used at baseline must be used for postbaseline measurements. BP parameters will be collected at a minimum of 2 readings per hour for 24-hour recordings. For ABPM assessments at baseline and Week 16, a repeat ABPM session must be performed if validity criteria are not met. Validity criteria are defined according to the European Society of Hypertension Guideline and include a minimum of 24 hours of readings with at least 70% of expected measurements (33 valid during the 24 hours); 20 valid awake (0900 to 2100); and 7 valid asleep (0100 to 0600) (O'Brien 2013). The time of the last dose of Androderm prior to the ABPM measurements will be recorded.

Term	Definition
Baseline ABPM	Any assessment recorded during the approximately 24-hour period starting on Screening Visit 3; after the ABPM device is applied, through Visit 1, when the ABPM device is removed
Week 16 (End of study intervention)	Any assessment recorded during the approximately 24-hour period starting on Visit 5, after the ABPM device is applied, through Visit 6/EOS/ET, when the ABPM device is removed
24-hour ABPM	Any assessment recorded at the specified analysis timepoint (baseline, Week 16) during the approximately 24-hour period after the ABPM device is applied through when the ABPM device is removed
Daytime ABPM	Any assessment recorded between 0900 and 2100 on either: • the day the ABPM device is applied • the day the ABPM device is removed
Night-time ABPM	Any assessment recorded between 0100 and 0600 on either: • the day the ABPM device is applied • the day the ABPM device is removed
Hours 0 through 23	For each Hour X, any assessment recorded between XX00 and XX59, on either: • the day the ABPM device is applied • the day the ABPM device is removed

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Physical examinations should be completed by a professionally trained physician or health professional listed on Form FDA 1572 and licensed to perform physical examinations.

8.2.2. Vital Signs

Vital signs will be assessed as follows:

- Oral temperature, and triplicate heart rate and cuff BP will be assessed.
- BP and pulse measurements will be assessed sitting with a completely automated device. Manual techniques will be used only if an automated device is not available.
- BP and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

- Vital signs (to be taken before blood collection for laboratory tests) will consist of 3 pulse and 3 BP measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute). All BP readings will be recorded on the eCRF.

8.2.3. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- At screening, the investigator or subinvestigator will assess the clinical significance of any values outside the reference ranges provided by the laboratory, and participants with abnormalities judged to be clinically significant will be excluded from the study.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significant during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
    - If laboratory values from non-protocol-specified laboratory assessments performed at a local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the AE eCRF.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs/SAEs from the signing of the ICF until the follow-up visit will be collected at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants.

Medical occurrences that begin before the start of study intervention, but after obtaining informed consent will be recorded in the AE section of the eCRF and will be considered pretreatment AEs.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Any AEs that are ongoing at the time of the final protocol-defined study visit will be followed until the condition returns to pre-study status, has resolved or stabilized, or can be explained as being unrelated to the study drug. If a follow-up visit is deemed necessary for appropriate safety surveillance, it will take place within 30 days of the final protocol-defined study visit.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.2. Method of Detecting AEs and SAEs

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to sponsor or designee within 24 hours of receipt of the information.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the package insert and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study intervention as per instructions in the protocol. Medication errors generally fall into 4 categories as follows:

- Wrong study drug/device
- Wrong dose (including dosing regimen, strength, form, concentration, amount)
- Wrong route of administration, including wrong site of administration (eg, wrong eye)
- Wrong participant (ie, not administered to the intended participant)

Medication errors include occurrences of overdose and underdose of the study intervention.

Overdose: Unintentional administration of a quantity of the study intervention given per administration or per day that is above the maximum recommended dose according to the reference safety information or protocol for the study intervention. This also takes into account cumulative effects due to overdose. In this study, overdose is defined as taking more than the assigned dose of study intervention.

Underdose: Unintentional administration of a quantity of the study intervention given per administration or per day that is under the minimum recommended dose according to the reference safety information or protocol. In this study, underdose is defined as taking less than the assigned dose of study intervention.

8.3.6. Adverse Events of Special Interest

1. Potential Hy's Law cases:

   - ALT or AST ≥ 3 × ULN and
   - Total Bilirubin ≥ 2 × ULN and
   - Alkaline Phosphatase < 2 × ULN

Anytime from the time the participant signs the ICF for the trial, until the final follow-up visit, investigators will notify the sponsor immediately when all the above criteria have been met. A potential Hy's law case will be sent directly to the sponsor by emailing IR-clinical-SAE@allergan.com on an AE of Special Interest Form along with the SAE Report Form as soon as possible (within 24 hours of learning of the potential Hy's Law). The CRF for potential Hy's law cases will be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities will be made, and close monitoring will be initiated in conjunction with the medical monitor and in accordance with the FDA "Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation" July 2009.

2. Prostate events:

   - Lower urinary tract symptoms of prostatic hyperplasia

Potential lower urinary tract symptoms of prostatic hyperplasia will be sent directly to the sponsor by emailing IR-clinical-SAE@allergan.com on an AE of Special Interest Form along with the SAE Report Form as soon as possible (within 24 hours of learning of the event). The CRF for lower urinary tract symptoms of prostatic hyperplasia will be completed within 7 calendar days.

8.4. Treatment of Overdose

For this study, any dose of Androderm greater than the assigned dose within a 24-hour time period will be considered an overdose.

Allergan does not recommend specific intervention for an overdose

In the event of an overdose, the investigator should:

1. Contact the medical safety physician immediately.
2. Closely monitor the participant for any AE/SAE and/or laboratory abnormalities.
3. Obtain a plasma sample for PK analysis if requested by the medical safety physician (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical safety physician based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Fasting morning serum total testosterone concentrations will be measured prior to ABPM device placement during the screening period on Screening Visit 3 (Day -3 to -1) and at Visit 5 (Day 112). The time of sample collection and ABPM device placement should be noted.

Fasting serum total testosterone concentrations will also be measured on Visit 2 (Day 14) and Visit 4 (Day 56), approximately 8 to 12 hours after application of the nightly dose on the previous night.

The serum total testosterone concentrations will be determined using a validated bioanalytical methodology.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers and Other Assessments

Biomarkers are not evaluated in this study.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

Health economics/Medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The null and alternative hypotheses for change from baseline in 24-hour average SBP obtained at baseline and Week 16 (Week 16 minus baseline) are as follows:

H_0: mE - mB $\geq$ 3.0 versus H_a: mE - mB < 3.0

Where mB and mE are mean 24-hour average SBP obtained at baseline and Week 16 respectively.

9.2. Sample Size Determination

Based on the FDA advice letter dated 24 May 2019, and the assumption that the mean difference in 24-hour SBP obtained at baseline and Week 16 is 0.0, with the upper bound of 3.0 mm Hg and the standard deviation of 10.0 mm Hg, 120 participants with available ABPM data at Week 16 will be required to provide 90% power to reject the null hypothesis at the 2 sided 5% significance level. Assuming a 25% dropout rate, 150 participants will be enrolled.

Approximately 300 participants will be screened, to achieve 150 enrolled who receive $\geq$ 1 administration of study intervention, for an estimated total of 120 evaluable participants.

9.3. Populations for Analyses

The analysis populations will consist of participants as defined below:

- The mITT population includes all participants with valid baseline ABPM session, who received $\geq$ 1 administration of study intervention, $\geq$ 1 post-treatment assessment for the primary ABPM endpoint, and at least 85% compliance to study intervention for the duration of the study.
- The safety population includes all treated participants who receive $\geq$ 1 administration of study intervention.
- The PK population includes all participants who have evaluable testosterone concentrations.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. General Considerations

The ABPM analyses will be based on the mITT population. Baseline is defined as the last nonmissing assessment before the first application of study intervention. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All CIs will be 2-sided 95% CIs, unless stated otherwise. No multiple comparison procedures will be applied.

9.4.1.1. Analysis Endpoints

The primary and secondary efficacy endpoints are listed below and analyses will be defined in the following sections. All analyses for other efficacy endpoints listed below will be defined in the SAP.

Primary efficacy endpoint:

- Change from baseline in 24-hour average SBP obtained at Week 16

Secondary efficacy endpoints:

- Change from baseline in 24-hour average DBP, MAP, pulse pressure, and heart rate obtained at Week 16

Other efficacy endpoints:

- Change from baseline in daytime average SBP, DBP, MAP, pulse pressure, and heart rate obtained at Week 16
- Change from baseline in night-time average SBP, DBP, MAP, pulse pressure, and heart rate obtained at Week 16
- Change from baseline over time (hourly average) by nominal clock time and time after dose: SBP, DBP, MAP, pulse pressure, and heart rate
- The status (yes or no) of participants with new anti-hypertensive medications
- The status (yes or no) of participants with dose increases in anti-hypertensive medications
- Outlier responder for participants meeting SBP $\geq$ 160 mm Hg for 24-hour average
- Outlier responder for participants meeting SBP change from baseline $\geq$ 20 mm Hg for 24-hour average
- Outlier responder for participants meeting DBP $\geq$ 100 mm Hg for 24-hour average
- Outlier responder for participants meeting DBP change from baseline $\geq$ 15 mm Hg for 24-hour average
- Status (yes/no) of participants with normalized testosterone concentrations at Week 16

9.4.1.2. Primary Analyses

Continuous descriptive statistics (n, mean, SD, median, min, max, Q1 and Q3) of 24-hour average SBP at baseline, Week 16, and change from baseline at Week 16 will be presented. Change from baseline at Week 16 will be tested using paired t-test, along with a 2-sided 95% CI.

If the upper bound of the two-sided 95% CI is less than 3.0, the alternative hypothesis of excluding an increase of 3 mm Hg in SBP will be inferred.

9.4.1.3. Secondary Analyses

Continuous secondary endpoints will be summarized by descriptive statistics (n, mean, SD, median, min, max, Q1 and Q3).

Categorical secondary and other endpoints will be summarized by number and percentage of participants in specified categories.

9.4.2. Safety Analyses

The safety analysis will be performed using the safety population and will be fully defined in the SAP. The safety parameters will include AEs, clinical laboratory, and vital signs. For each of the clinical laboratory and vital signs parameters, the last nonmissing safety assessment before the first dose of study intervention will be used as the baseline for all analyses of that safety parameter.

9.4.2.1. Adverse Events

An AE will be considered a TEAE if the AE began or worsened (increased in severity or became serious) on or after the date (and time, if known) of the first dose of study intervention. However, an AE that occurs more than 30 days after the last dose of study intervention will not be counted as a TEAE.

An AE will be considered a TESAE if it is a TEAE that additionally meets any SAE criterion.

The number and percentage of participants with TEAEs during the study will be tabulated by system organ class and preferred term and by system organ class, preferred term, and severity.

The number and percentage of participants with treatment-related TEAEs during the study will be tabulated by system organ class and preferred term.

If more than 1 AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarizations by severity and by relationship to study intervention.

Summary tables will be provided for participants with TESAEs and participants with TEAEs leading to discontinuation if these occurred in 5 or more participants. Listings of all AEs, SAEs, and AEs leading to discontinuation by participant will be presented.

The definitions of an AE and SAE can be found in Appendix 3.

9.4.2.2. Clinical Laboratory Assessments

Descriptive statistics for clinical laboratory values (in SI units) at baseline (screening) and changes from baseline at each assessment will be presented for each clinical laboratory assessment.

The criteria for PCS laboratory values will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated at each assessment. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

9.4.2.3. Vital Signs

Descriptive statistics for vital signs (systolic and diastolic cuff BP, heart rate, weight, and temperature) at baseline (screening) and changes from baseline at each assessment will be presented.

Vital signs values will be considered to be PCS if they meet both the observed-value criteria and the change-from-baseline-value criteria that will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline vital signs values will be tabulated for each assessment. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

9.4.3. PK Analyses

Fasting morning serum total testosterone concentrations will be measured prior to ABPM device placement during the screening period on Screening Visit 3 (Day -3 to -1) and at Visit 5 (Day 112). The time of sample collection and ABPM device placement should be noted.

Fasting serum total testosterone concentrations will also be measured on Visit 2 (Day 14) and Visit 4 (Day 56), approximately 8 to 12 hours after application of the nightly dose on the previous night.

Concentrations below the limit of quantitation will be treated as 0 for all PK calculations. Descriptive statistics for testosterone concentrations will be provided at each sampling timepoint for all participants in the PK population. Details of the statistical analyses of PK data will be described in the analysis plan finalized prior to database lock.

9.4.4. Other Analyses

In addition to the analysis method described in Section 9.4, all exploratory analyses will be described in a separate SAP. Graphical summaries may include:

- Box plot of hourly average for both SBP and DBP at baseline and at endpoint

- Cumulative distribution function curves of 24-hour average SBP and DBP at baseline and postbaseline
- Forest plots for change from baseline SBP and DBP of daytime, night-time and 24-hour average

9.4.4.1. Subgroup Analyses

Sensitivity analyses on the primary endpoint, secondary endpoints, and graphical summaries will be conducted on the following subgroups:

- Participants without baseline medical history of hypertension
- Participants with treated baseline medical history of hypertension
- Participants with untreated baseline medical history of hypertension

9.5. Interim Analyses

There is no interim analysis planned for the study.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the CIOMS International Ethical Guidelines
  - Applicable ICH/ISO GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, package insert, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the overall conduct of the study by the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

10.1.2. Financial Disclosure

Investigators 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. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that signed informed consent was obtained before the participant was enrolled in the study and the date the signed consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; any identifiable participant information will only be transferred in accordance with the signed Informed Consent provisions.
- The participant must be informed that his personal study-related data will be used by the sponsor in accordance with local privacy and data protection laws. The level of disclosure must also be explained to the participant who will be required to give consent for their personal data to be used as described in the informed consent.
- The participant 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.
- Management of privacy incidents relating to clinical trial participant personal data, as well as handling of data participant rights requests (if applicable), should be handled in accordance with the agreed upon CTA provisions.

10.1.5. Dissemination of Clinical Study Data

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

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as stated in the clinical trial agreement. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed by the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source data are defined as: original documents, data, and records (eg, hospital records, clinical and office charts, diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study). These records include, but are not limited to, original signed and dated consent forms, relevant observations including records of AEs, and records of all exposure to study intervention.

10.1.8. Study and Site Start and Closure

For the purpose of clinical trial registries, the study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up. If a premature termination or suspension occurs, the sponsor shall remain responsible for providing resources to fulfill the protocol obligations and existing agreements for follow-up of participants enrolled in the study, and each investigator or authorized designee shall promptly inform enrolled participants, if applicable.

10.1.9. Publication Policy

- Allergan as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.10. Compliance with Protocol

The investigator is responsible for compliance with the protocol by the investigational site. A representative of the sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits by the site to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10-1 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10-1 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count RBC count Hemoglobin Hematocrit PT INR	RBC indices: MCV MCH MCHC %Reticulocytes	WBC count with differential (absolute): Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry	BUN Creatinine Glucose, fasting HbA1c Prolactin	Potassium Sodium Calcium PSA	AST ALT Alkaline phosphatase Fasting morning total testosterone	Total, direct and indirect bilirubin Total protein Cholesterol, chloride, albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			

Investigators must document their review of each laboratory safety report.

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

10.3.1. Definition of AE

AE Definition

• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
• NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
• **Adverse Event of Special Interest**
• An AESI (serious or nonserious) is one of scientific and medical concern specific to the sponsor's study intervention or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and understand it.
• The following AESI(s) have been identified for the study intervention(s) in this protocol:
  • Potential Hy's Law cases
  • Prostate events
• Serious AESIs should be reported to the sponsor within 24 hours via the SAE form. Nonserious AESIs should be recorded in a timely fashion on the appropriate page of the eCRF.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease); for example:
  ○ The test result is associated with accompanying symptoms, and/or
  ○ The test result requires additional diagnostic testing or medical/surgical intervention, and/or
  ○ The test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
  ○ The test result is considered to be an AE by the investigator or sponsor.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is a suspected transmission of any infectious agent via a medicinal product

g. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the sponsor or designee AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity
The investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to one of the following categories: • Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities or daily living. • Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. • Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee. • The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.
Follow-up of AEs and SAEs
• See Section 8.3.3.

10.3.4. Reporting of SAEs

SAE Reporting to Sponsor or Designee Within 24 Hours
• Contacts for SAE reporting can be found on the protocol title page. • Email is the preferred method to transmit SAE information. • Facsimile transmission of the SAE information is also acceptable. • In rare circumstances and in the absence of facsimile equipment, notification by telephone (see the study contact list) is acceptable with a copy of the SAE form, sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames.

10.4. Appendix 4: Abbreviations

Abbreviation	Definition
ABPM	ambulatory blood pressure monitoring
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
DBP	diastolic blood pressure
DHEA	dehydroepiandrosterone
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	Independent Ethics Committee
INR	international normalized ratio
I-PSS	International Prostate Symptom Score
IRB	Internal Review Board
ISO	International Organization for Standardization
IUD	intrauterine device
IUS	intrauterine system
MAP	mean arterial pressure
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration

Abbreviation	Definition
MCV	mean corpuscular volume
mITT	modified intent-to-treat
N/A	not applicable
NCI	National Cancer Institute
PCS	potentially clinically significant
PK	pharmacokinetic
PSA	prostate specific antigen
PT	prothrombin time
Q1	quartile 1
Q3	quartile 3
RBC	red blood cell
S1	Screening Visit 1
S2	Screening Visit 2
S3	Screening Visit 3
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
TC	teleconference
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
V1	Intervention Period Visit 1
V2	Intervention Period Visit 2
V3	Intervention Period Visit 3
V4	Intervention Period Visit 4
V5	Intervention Period Visit 5
V6	Intervention Period Visit 6
WBC	white blood cell

10.5. Appendix 5: Standard Discontinuation Criteria

This table provides participant discontinuation criteria for this protocol. CDISC terminology is used, and thus *subject* or *patient* is used instead of *participant* (as used elsewhere in this protocol). These terms are interchangeable.

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (modified from ICH E2A) Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion (NCI)
Death	The absence of life or state of being dead (NCI)
Disease relapse	The return of a disease after a period of remission
Lack of efficacy	The lack of expected or desired effect related to a therapy (NCI)
Lost to follow-up	The loss or lack of continuation of a subject to follow-up
Non-compliance with study drug	An indication that a subject has not agreed with or followed the instructions related to the study medication (NCI)
Other	Different than the one(s) previously specified or mentioned (NCI)
Physician decision	A position, opinion, or judgment reached after consideration by a physician with reference to subject (NCI)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Screen failure	The potential subject who does not meet one or more criteria required for participation in a trial
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
Technical problems	A problem with some technical aspect of a clinical study, usually related to an instrument (NCI)
Withdrawal by subject	An indication that a study participant has removed itself from the study (NCI)

10.6. Appendix 6: Study Tabular Summary

This table is intended for use in posting study information to registries (eg, ClinicalTrials.gov).

Parameter Group	Parameter	Value
Trial information	Trial Title	A Phase IV, Multi-center, Open-label, Single-arm 24-hour Ambulatory Blood Pressure Monitoring (ABPM) Study of 16 Weeks Treatment with Androderm® in Hypogonadal Men
	Clinical Study Sponsor	Allergan
	Trial Phase Classification	Phase 4 trial
	Trial Indication	Hypogonadism
	Trial Indication Type	Treatment
	Trial Type	Safety
	Trial Length	19 weeks
	Planned Country of Investigational Sites	United States
	Planned Number of Subjects	150
	FDA-regulated Device Study	No
	FDA-regulated Drug Study	Yes
	Pediatric Study	No
Subject information	Healthy Subject Indicator	No
	Planned Minimum Age of Subjects	18
	Planned Maximum Age of Subjects	80
	Sex of Participants	Males
	Stable Disease Minimum Duration	N/A
Treatments	Investigational Therapy or Treatment	Androderm
	Intervention Type	Drug
	Dose per Administration	2 mg, 4 mg, or 6 mg
	Dose Units	
	Dosing Frequency	once daily
	Route of Administration	transdermal system
Trial design	Study Type	Interventional
	Intervention Model	Single-group
	Planned Number of Arms	1
	Trial Is Randomized	No
	Trial Blinding Schema	Open-label
	Adaptive Design	No

10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Contraception Guidance:

Male Participants

Nonvasectomized male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined timeframe in Section 5.1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
- Agree to use a male condom with spermicide plus partner use of a contraceptive method with a failure rate of < 1% per year as described in Table 10-2 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

In addition, nonvasectomized male participants must refrain from donating sperm for the duration of the study and for 30 days after the last dose of study intervention.

Nonvasectomized male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined timeframe.

Table 10-2 Highly Effective and Acceptable Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of < 1% per year when used consistently and correctly*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • IUD • IUS • Etonogestrel implant (ie, Nexplanon®) • Bilateral tubal occlusion (eg, Essure®, bilateral tubal ligation) • Intrauterine copper contraceptive (ie, ParaGard®)

Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
Acceptable Methods *Acceptable birth control methods that result in a failure of more than 1% per year include:*
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cap, diaphragm, or sponge with spermicide • Nonhormonal intrauterine device A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be used during the study intervention period and for at least 30 days after the last dose of study intervention.

Collection of Pregnancy Information:

Male Participants with Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

11. References

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