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Protocol for Study M19-161

24-Hour ABPM in Hypogonadal Men on TRT

VERSION:	3.0	DATE:	26 August 2020
SPONSOR:	AbbVie Inc.*	NUMBER OF SITES:	Approximately 45 sites in the United States
ABBVIE INVESTIGATIONAL PRODUCT:	AndroGel® (testosterone gel) 1.62%	EudraCT:	Not applicable

FULL TITLE: 24-Hour Ambulatory Blood Pressure Monitoring Study in Hypogonadal Men Receiving Testosterone Replacement Therapy

Incorporating Versions 1.0, 2.0 and 3.0

PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

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1 SYNOPSIS

Title: 24-Hour Ambulatory Blood Pressure Monitoring Study in Hypogonadal Men Receiving Testosterone Replacement Therapy	
Background and Rationale:	This study is a postmarketing requirement to assess the effect of AndroGel 1.62% on blood pressure (BP).
Objective(s) and Endpoint(s):	To assess the effect of AndroGel 1.62% on BP. The primary endpoint is the change in 24-hour average systolic blood pressure (SBP) from Baseline to End of Treatment (EOT).
Investigator(s):	Investigator information on file at AbbVie
Study Site(s):	Approximately 45 sites in the United States
Study Population and Number of Subjects to be Enrolled:	Approximately 190 hypogonadal men ≥ 18 years of age at the time of enrollment.
Investigational Plan:	This is a multicenter, Phase 4, open-label, single-arm study to establish the non-inferiority with a margin of 3 mmHg for change in 24-hour average SBP from Baseline to EOT.
Key Eligibility Criteria:	Hypogonadal men with BP > 100/60 mmHg and < 140/90 mmHg
Study Drug and Duration of Treatment:	AndroGel 1.62% once daily for at least 16 weeks.
Date of Protocol Synopsis:	26 August 2020

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Testosterone (T) products have been approved in the United States (US) for over 50 years for the treatment of T-deficient men. These products are currently indicated for the treatment of congenital or acquired primary hypogonadism and hypogonadotropic hypogonadism in men.[1,2]

Hypogonadism is an endocrine disorder characterized by absent or deficient T levels along with signs and symptoms of androgen deficiency, including delayed development or regression of secondary sexual characteristics, impaired sexual function, impaired sense of well-being, depressed mood, decreased muscle strength associated with a loss of muscle mass, and reduced bone mineral density (BMD).[2-7]

The efficacy of AndroGel 1.62% is demonstrated by its ability to increase serum total T levels by the absorption of T through the skin when applied topically. The objective of testosterone replacement therapy (TRT) in hypogonadal men is to replace T within the eugonadal range for healthy men (300 to 1000 ng/dL). Replacement of T levels into the eugonadal range in hypogonadal men should lead to restoration of androgenic effects such as improvements in libido and mood, increased lean mass, decreased fat mass and increased BMD.[2] The aforementioned endpoints have been examined in placebo-controlled studies with various levels of supportive evidence depending on the cohorts (hypogonadal, eugonadal, mixed).

Current guidelines for the use of TRT outline the appropriate assessment and monitoring of men who are candidates for T therapy. Key components of the Endocrine Society Guidelines[8] include criteria for selecting candidates with signs and symptoms consistent with hypogonadism and documented evidence of low T levels, for whom TRT may be indicated. The Endocrine Society Guidelines also offer recommendations for confirmatory testing of serum T concentrations, additional evaluation, and TRT.[8]

Effects of Testosterone on Blood Pressure

Testosterone-related research evaluating effect of T on Blood pressure (BP) includes preclinical and in vitro experiments, as well as some clinical data.[9,10]

Testosterone-related effects include:

- Increased nitric oxide synthase;[11]
- Decreased endothelin-1 in humans, although opposite effects seen in animals;[12]
- Improved endothelial function;[13,14]
- Decreased prostacyclin;[15]
- Increased thromboxane (TXA)[16] postorchiectomy in rats appears to negatively affect nitric oxide and TXA release, demonstrating the complex relationship between factors influenced by hypogonadism itself (i.e., castration in this instance established a microenvironment where TXA

would be expected to cause more vasoconstriction) versus changes induced by TRT in hypogonadal men;[17]

- Sodium retention: the mechanism is unclear, may occur through activation of the renin-angiotensin system.[18,19]

Blood Pressure Changes in TRT Clinical Trials

Data from trials using a variety of T formulations and routes of administration demonstrate variable BP responses to therapy. The results observed range from a modest detriment to a benefit, including neutral effects.

In general, transdermal TRT does not appear to adversely influence overall study cohort mean BP across a number of studies and across a variety of patient types, including men at increased risk for cardiovascular disease (e.g., men with diabetes, traditional cardiovascular risk factors, and older age). However, BP increases have been observed with oral TRT.[20]

The objective of the present study is to evaluate the effect of AndroGel 1.62% on BP in hypogonadal men to fulfill a postmarketing requirement from the US Food and Drug Administration (FDA).

Ambulatory Blood Pressure Monitoring

Ambulatory Blood Pressure Monitoring (ABPM) has been widely used for the past decade in research and clinical practice around the world;[21-23] however, its use has been limited in the US because of the expense of the equipment and the time involved in patient training and data analysis.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,[24-26] summarizes the use of ABPM as follows:

- ABPM provides information about BP during daily activities and sleep.
- ABPM is warranted for evaluation of "white coat" hypertension in the absence of target organ injury. It is also helpful to assess patients with apparent drug resistance, hypotensive symptoms with antihypertensive medications, episodic hypertension, and autonomic dysfunction.
- ABPM provides a measure of the percentage of BP readings that are elevated of the overall BP load, and of the extent of BP reduction during sleep. In most individuals, BP decreases by 10% to 20% during the night; those in whom such reductions are not present are at increased risk for cardiovascular events, and ABPM helps to identify these individuals.

A great deal of evidence has accumulated in the past decade regarding ABPM utility. It has been demonstrated that ABPM is a better indicator of a patient's true BP and correlates more closely with target organ damage and cardiovascular events than clinical cuff measurements. As a result, ABPM is now considered to be the noninvasive gold standard.[27]

Rationale for an ABPM Study of Testosterone in Hypogonadal Men

The rationale for such a study includes data for a signal of hypertension risk in men treated with oral T, and that relatively few TRT studies have used ABPM to monitor BP in hypogonadal men treated with T.

ABPM Validity Criteria

Data presented at the public workshop titled "Evaluating the Pressor Effects of Drugs & ABPM Studies" in February 2019 demonstrated that 50% of expected measurements during 24 hours within an individual along with other criteria may be sufficient for ABPM to be considered valid in the research trial settings.[28]

The ABPM validity criteria for present study are outlined below in Section 4.1 and in Appendix 7.1 of the Operations Manual.

2.2 Benefits and Risks to Subjects

Benefits/Risks of Testosterone Replacement Therapy

The efficacy of AndroGel 1.62% is demonstrated by its ability to increase serum total T levels by the absorption of T through the skin when applied topically.

Potential risks of treatment with AndroGel 1.62% include secondary transfer of T to others, increased prostate-specific antigen (PSA) levels, prostate cancer, mood swings, hematocrit (Hct) increase, and skin irritation at the application site. For further details, please see findings from completed studies, including safety data in the current AndroGel 1.62% package insert.[29]

Benefits/Risks of ABPM

Ambulatory blood pressure monitoring provides information that home BP and clinic BP cannot, including:

- An estimate of true, or mean, BP level;
- Addresses BP variability;
- Allows for evaluation of diurnal rhythm of BP;
- Allows for measuring nighttime BP as nighttime hypertension correlates with a higher risk of cardiovascular end outcomes;
- Allows for ruling out white-coat hypertension;
- Allows for conducting BP medication assessment.

Ambulatory blood pressure monitoring is especially useful for recently diagnosed hypertension or the assessment of BP medications effectiveness. An ABPM test can help physicians to prescribe the right medications to keep BP in control and reduce future cardiovascular risk. When ABPM is incorporated into the hypertension diagnostic and treatment process, up to a 14% savings in the cost of healthcare has been calculated.[30]

Although subjects may not directly benefit from the ABPM procedure, their participation in the study may contribute to scientific advances in the area of ABPM research and its clinical practice, as well as provide valuable information for the medical community and hypogonadal men receiving TRT.

The risks of ABPM are very low. One prospective case series study demonstrated that only 4 of 219 patients had complications during ABPM. The most frequent complications were peripheral petechiae, which could be related to underlying vascular abnormalities.[31]

3 OBJECTIVES AND ENDPOINTS

3.1 Objective

The objective of this study is to assess the effect of AndroGel 1.62% on BP. The hypothesis corresponding to the primary objective is that AndroGel 1.62%, used as labelled, does not affect 24-hour average systolic blood pressure (SBP).

3.2 Primary Endpoint

The primary endpoint is the change in 24-hour average SBP from Baseline to End of Treatment (EOT).

3.3 Other Endpoints

- Change from Baseline to EOT in average daytime (09:00 – 21:00 h) mean arterial pressure (MAP), SBP, diastolic blood pressure (DBP), pulse pressure (PP), and heart rate (HR)
- Change from Baseline to EOT in average nighttime (01:00 – 06:00 h) MAP, SBP, DBP, PP, and HR
- Change from Baseline to EOT in average 24-hour MAP, DBP, PP, and HR
- Change from Baseline to EOT of MAP, SBP, DBP, PP, and HR at the time of maximum observed T concentration (T_{max}) by 24-hour recordings
- Change from Baseline over time (hourly average) by nominal clock time for MAP, SBP, DBP, PP, and HR by 24-hour recordings at EOT
- Change from Baseline over time (hourly average) by time after dose for MAP, SBP, DBP, PP, and HR by 24-hour recordings at EOT
- Subjects with new concomitant antihypertensive medication(s) during the Treatment Period
- Subjects with dose increases in antihypertensive medication(s) during the Treatment Period
- Subjects and observations meeting the following BP thresholds separately by 24-hour average and by hourly average by 24-hour recordings:
  - ≥ 160 mmHg SBP at EOT
  - ≥ 100 mmHg DBP at EOT
  - ≤ 90 mmHg SBP at EOT
  - ≤ 60 mmHg DBP at EOT
  - ≥ 20 mmHg increase from Baseline to EOT in SBP
  - ≥ 15 mmHg increase from Baseline to EOT in DBP

3.4 Safety Endpoints

Safety will be assessed by the incidence of serious adverse events (SAEs), adverse events of special interest (AESI), study procedure–related nonserious adverse events (AEs) and SAEs, and AEs that lead to study drug discontinuation. In addition, changes from Baseline in laboratory and vital sign parameters to each specified timepoint will be summarized.

3.5 Pharmacokinetic Endpoints

The steady-state pharmacokinetics (PK) of T will be characterized at the EOT Visit after a valid Week 16 ABPM 24-hour collection from serial PK blood samples (4 in total) obtained in all subjects at 0 hour (immediately prior to subject on-site application of study drug), and at 2 hours, 4 hours, and between 6 to 8 hours following study drug application. The time of on-site application of study drug and time of PK blood draws will be recorded by the site for each subject.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a multicenter, Phase 4, open-label, single-arm study to establish the non-inferiority with a margin of 3 mmHg for change in 24-hour average SBP from Baseline to EOT. Efficacy will not be evaluated in this study.

The initial planned study enrollment is approximately 190 subjects based on the projected sample size calculation and subject discontinuation rate. There will be approximately 45 sites in the US.

The Screening Period is up to 45 days prior to the baseline ABPM 24-hour collection and includes 2 separate visits (Screening Visit 1 [SV1] and Screening Visit 2 [SV2]) to establish subject eligibility. Office BP measurements by automated oscillometric device (see Appendix 7.2 of the Operations Manual) will be used for evaluation of the subject for BP eligibility criteria at Screening. Once subjects meet all of the eligibility criteria during Screening, they will be enrolled into the study and followed until approximately 30 days following EOT.

EOT is defined as a valid ABPM 24-hour collection after at least 16 weeks of treatment with AndroGel 1.62%. End of study (EOS) is defined as last visit/last procedure/last contact (office visit or phone call).

Ambulatory blood pressure monitoring measurements will be obtained from all subjects using a portable data-monitoring device. The ABPM procedure will be performed over a 24-hour period across 2 days and will include ABPM device application by site (1st Day) and ABPM device removal by site (2nd Day).

The validity of the ABPM 24-hour collection measurements will be evaluated prior to performing the procedures for the Day 1 Visit, and prior to performing the procedures for the EOT Visit. Day 1 is

defined as start of treatment (first dose of the study drug). Subjects will receive the first dose of the study drug on site only after validity of the baseline ABPM 24-hour collection is confirmed.

The investigator or designee will assess the validity of ABPM measurements based on the results that are immediately available on site once data is downloaded from the ABPM device, to the study configured laptop, utilizing ABPM specific software. The investigator or designee can then assess if a repeat ABPM collection is required.

The ambulatory blood pressure (ABP) monitor will be set to automatically measure and record BP every 30 minutes for 24 hours. The ABPM 24-hour collection will be repeated if > 50% of collected ABPM data (measurements) during the 24-hour period, daytime period (09:00 – 21:00 h), or nighttime period (01:00 – 06:00 h) are missing or if there is an ABPM device malfunction. Based on these criteria, a 24-hour ABPM collection will be considered valid if all of the following are obtained:

1. At least 24 measurements of SBP during the 24-hour period
2. At least 12 SBP measurements between 09:00 and 21:00
3. At least 5 SBP measurements between 01:00 and 06:00

The repeat ABPM 24-hour collection will be conducted at Unscheduled Visits within 7 days of the invalid APBM. The recorded ABPM data will be transmitted to the core lab for centralized management (see Section 3.14 of the Operations Manual).

The study team, study statistician, study sites, and subjects will remain masked to the Week 16 ABPM data until the end of the Treatment Period of the last subject.

The Treatment Period will last for at least 16 weeks. The site will record dosing times corresponding to the visits for ABPM collection and serial PK sampling times. Titration evaluation of T dose will occur in all subjects at Week 2 and Week 4. All subjects will start on 40.5 mg of study drug. Subjects will return on Weeks 2 and 4 to have early morning pre-dose T levels evaluated for titration. Subjects will be titrated up by 20.25 mg, down by 20.25 mg, or remain on the previously assigned dose if their serum T levels are < 350 ng/dL, > 750 ng/dL, or between 350 ng/dL and 750 ng/dL inclusive, respectively (see Table 2 in Section 6.4 of the Operations Manual). The final titrated doses will be 20.25 mg, 40.5 mg, 60.75 mg, or 81.0 mg, and subjects will remain on their final titrated dose following the Week 4 assessment until EOT. The Week 10 Visit will be a telephone call only.

Subjects will continue on study drug until after a valid ABPM 24-hour collection has been confirmed and will apply the study drug on site before the serial PK sampling at the EOT Visit. The serial PK blood samples will be drawn only after validity of the ABPM 24-hour collection has been confirmed.

A Follow-up Visit phone call will occur approximately 30 days after the last dose of study drug. During phone calls and in-person visits throughout the study, subjects will be asked specific questions pertaining to the possible occurrence of SAEs, AESI, as well as the collection of additional information related to ongoing AE(s).

Any change in antihypertensive medication(s), antihypertensive medication(s) dose increase and/or initiation of antihypertensive medication(s) will be documented throughout the study.

Section 3.11 of the Operations Manual (Appendix E) provides details on the clinical laboratory samples collection during the study.

The study schematic is shown in Figure 1. Further details regarding study procedures are outlined in the Operations Manual. See Section 5 for information regarding eligibility criteria.

An analysis to estimate the standard deviation (SD) of change from Baseline in SBP average 24-hour recording will be conducted in a blinded fashion when approximately 70% of the planned subjects in the per protocol population (i.e., 120 subjects) have completed the EOT Visit. The objective of this analysis is to re-estimate sample size if needed.

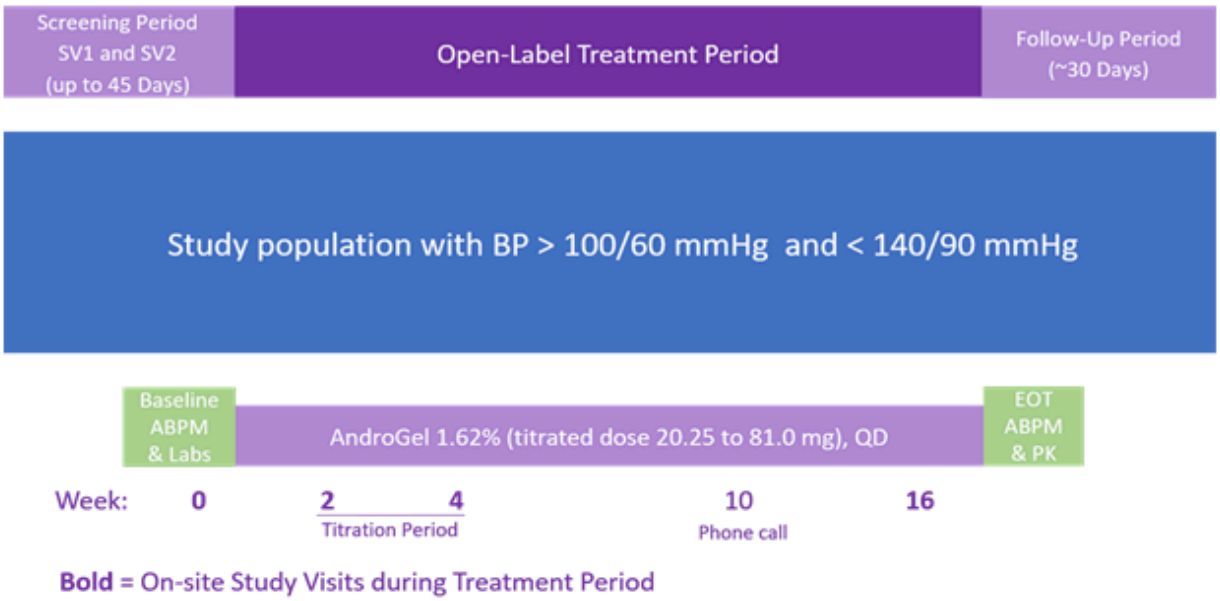
AbbVie or its designee will make every effort to give sites advanced notice when recruitment for the study is nearing completion to minimize the risk for subjects in Screening who may not be allowed to enroll in the study.

Rescreening

Subjects who fail to meet the eligibility criteria may be rescreened one time at the investigator's discretion once their clinical status changes.

Men with a SV1 T level between 300 and 333 ng/dL or men who did not have a confirmed T level < 300 ng/dL at SV2 can be rescreened after 3 months (90 days) following the visit (SV1 or SV2) at which T was measured and did not meet eligibility criteria of < 300 ng/dL. All of the Screening procedures must be repeated, and the subjects must be re-consented. Rescreened subjects will use the originally assigned subject number.

Figure 1. Study Schematic



ABPM = ambulatory blood pressure monitoring; BP = blood pressure; EOT = End of Treatment; PK = pharmacokinetics; QD = once a day; SV1 = Screening Visit 1; SV2 = Screening Visit 2

4.2 Discussion of Study Design

Choice of Control Group

Not applicable.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All clinical and laboratory procedures in this study are standard and generally accepted.

American Heart Association (AHA) recommendations for measurement of BP will be followed throughout the study. Investigators or their designees responsible for obtaining BP measurements will complete training in AHA recommendations prior to initiating the study,[32] as well as training in cuff size measurements and ABPM measurements prior to study initiation.

Justification of study design

An important difference between conventional and ambulatory BP measurement is the absence of a placebo effect with the latter that has been demonstrated in numerous studies.[33-43] Fitzgerald et al also postulated that ambulatory BP measurements do not regress to the mean; hence subjects with high BPs do not exhibit a decrease in BP and those with low BPs do not show a tendency to raise their pressure with repeated measurements.[44]

In February 2019, results from the FDA's ABPM research database review were presented at a public workshop titled, "Evaluating the Pressor Effects of Drugs & ABPM Studies." The review was aimed to evaluate the consistency of the BP change from Baseline to post-baseline in placebo arms across multiple ABPM studies. The data from 11 placebo-controlled ABPM studies (456 subjects) showed that the mean estimate for 24-hour change in SBP was around zero across the number of ABPM studies, with no significant difference in BP change between Baseline and post-baseline placebo visits.[28]

The reported lack of placebo effect in ABPM placebo-controlled trials implies that ABP measurements taken before and repeated after the Treatment Period in a single-arm open-label trial design may be adequate for evaluation of the effect of the study drug on BP without using placebo arm.

Standard deviation

The only ABPM data for subjects treated with topical T are available from a Phase 3 study that compared oral T with topical T. The ABPM demonstrated the mean increase of 0.2 (± 9.4) mmHg in 24-hour average SBP from Baseline to Visit 6 for topical T and 4.9 (± 8.7) mmHg increase for oral T. The SD for 24-hour SBP for both oral and topical T in this trial was slightly below 10 mmHg. Similar results were observed for MAP and PP.[45] The data from this study supports the choice of the open-label single-arm trial design over other designs for this protocol, and justifies the study assumption of SD of 10 mmHg for 24-hour SBP.

Suitability of Subject Population

Eligible subjects are hypogonadal men 18 years of age or older at the time of enrollment who have low serum T, signs or symptoms that are associated with hypogonadism, and who may benefit from therapeutic intervention by raising and maintaining their T concentrations within the normal range.

Confirmation of T values below normal limits will be conducted during Screening. Subjects either will be naïve to T therapy or have not been treated with T in the past 6 months. Men for whom T therapy is contraindicated such as those with history of prostate or breast cancer, unprovoked pulmonary embolism (PE), unprovoked deep vein thrombosis (DVT), polycythemia, and those seeking fertility will be excluded. See Section 5 for information regarding eligibility criteria.

Justification of the study population age group and comorbid conditions

In 2014 in preparation for the TRT Advisory Committee meeting, the TRT Sponsors assessed the age distribution and comorbid conditions of patients receiving T therapy by evaluating available literature and conducting data analysis.

The data showed that men 45 to 64 years of age received the highest number of prescriptions (approximately 60%), a trend that has not changed in the past few years. Men younger than 45 years represented approximately 19% of prescriptions, while men older than 65 years represented approximately 21% of prescriptions.

The characteristics of the patient population receiving T therapy, comorbidities in particular, were evaluated in a study of 10,159 patients treated with TRT using the data from the Kaiser Permanente system. Most frequent diagnoses were as follows: 43.7% of the patient population had hypertension, 43.1% had hyperlipidemia, 33.5% had erectile dysfunction, 26.7% had testicular dysfunction, and 20.3% had diabetes.[46]

In the Testim® Registry, which included men with hypogonadism at BL, 36.7% of men were determined to have metabolic syndrome, 19.8% had hypertension, 19.9% had dyslipidemia, 17.9% had coronary artery disease, and 12.5% had diabetes.[46,47]

Based on these data, the expected ABPM subject population for the present study will consist of men, with the majority in the age group of 45 to 64 years. Up to 45% of the subject population will have hypertension and up to 20% will have diabetes.

Blood Pressure Variability

It has long been known that BP is characterized by an array of spontaneous variations. Blood pressure values vary markedly within the 24 hours in response to physical activity, sleep, and emotional stimuli of various nature and duration.[48-51]

Blood pressure variability is different in normotensive patients with normal 24-hour BP from that in patients with hypertension. Mancia et al demonstrated that the absolute short- and long-term BP variabilities were lowest in normotensive subjects and greatest in severe hypertensive subjects for systolic, diastolic, and MAPs.[52]

To balance BP variability in normotensive and hypertensive subjects and to assure adequate representation of the subject population with cardiovascular risk profile of men using marketed TRT, an Interactive Response Technology (IRT) system will categorize the subjects by ongoing medical history of hypertension (Yes/No) at Baseline. Enrollment caps will be employed to ensure that 35% to 50% of subjects with an ongoing medical history of hypertension are enrolled.

Selection of Doses in the Study

All doses utilized in the study are per the product label of AndroGel 1.62%.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects must voluntarily sign and date an informed consent, approved by an institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.
- 2. Able to understand and adhere to protocol requirements, restrictions and instructions (per investigator's judgment).

Demographic and Laboratory Assessments

- 3. Hypogonadal men ≥ 18 years of age at the time of enrollment. Hypogonadism is defined as:

- Presence of at least one of the following symptoms that may be related to low T values and is/are consistent with hypogonadism (confirmed prior to obtaining T levels):
  - Decreased sexual desire or libido
  - Decreased spontaneous erections (e.g., morning erections)
  - Decreased energy or fatigue/feeling tired
  - Low mood or depressed mood
  - Loss of body (axillary and pubic) hair or reduced shaving
  - Hot flashes

AND

- Confirmed by 2 serum T levels < 300 ng/dL by blood samples drawn at least 48 hours apart. These samples should be obtained between 5 am and 11 am local time.

- 4. Laboratory values meeting the following criteria within the Screening Period prior to the first dose of study drug:
  - Hematocrit (Hct) < 50%
  - Alanine aminotransferase and aspartate aminotransferase < 3 × upper limit of normal
  - PSA ≤ 3.0 ng/mL or PSA ≤ 1.5 ng/mL in men treated with 5-alpha reductase inhibitors (e.g., dutasteride, finasteride)
- 5. Office BP measurements > 100/60 mmHg and < 140/90 mmHg at both Screening Visits (SV1 and SV2).
- 6. If on any antihypertensive therapy, such therapy must be stable for at least 4 weeks before SV1.
- 7. No history of:
  - Upper arms and shoulders with current or recurrent ulcer, erosion, lichenification, inflammation psoriasis, eczema or use of topical corticosteroids on the upper arms and shoulders
  - Tattoo application or removal in the region of study drug application within 6 months of Screening
  - Any T replacement, clomiphene, compounded or over-the-counter (OTC) androgenic steroid derivatives, and dehydroepiandrosterone, including investigational products that may affect the reproductive hormonal system, within the past 26 weeks prior to and during Screening through EOT
  - Untreated, severe obstructive sleep apnea
  - Unprovoked DVT, unprovoked PE, or known thrombophilia
  - Polycythemia vera or secondary polycythemia, such as polycythemia due to untreated sleep apnea or severe chronic obstructive pulmonary disease
  - Prostate or breast cancer

- Any active malignancy
- Any in-subject hospitalizations (duration of hospitalization > 24 hours) or major febrile illness (temperature > 101°F) within 4 weeks prior to, during screening, and at the time of enrollment

- 8. No history of clinically significant (per investigator's judgment) drug or alcohol abuse (including illicit steroid use) within the last 12 months prior to Screening.
- 9. No history of clinically significant medical conditions or any other reason that the investigator determines would interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive study drug.
- 10. No history of known skin intolerance to alcohol or allergy to any of the ingredients of the study drug (see AndroGel 1.62% prescribing information).
- 11. No Severe (New York Heart Association Functional class III or IV) heart failure, or known ejection fraction ≤ 35% are present, atrial fibrillation or other serious arrhythmia that may affect ABP measurements.
- 12. Subject does not work night shifts or is not otherwise required to perform strenuous manual labor while wearing the ABPM monitor.
- 13. Subject's upper arm circumference is < 50 cm.

Contraception

- 14. Subject is not considering fathering a child or donating sperm during the study or for approximately 30 days after the last dose of study drug.

Concomitant Medications

- 15. Subject must not have been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another clinical study.

5.2 Contraception Recommendations

Contraception Requirements for Males

Male subjects who are sexually active with a female partner of childbearing potential must agree to use condoms, even if the male subject has undergone a successful vasectomy, from Baseline through at least 30 days after the last dose of study drug.

5.3 Prohibited Medications and Therapy

Subjects must not take oral nitrates concomitantly with drug products used to treat erectile dysfunction (e.g., tadalafil, sildenafil citrate, vardenafil hydrochloride).

Subjects must not take any other form of T other than the study drug during the study as well as the following prohibited medications:

- Compounded or OTC androgenic steroid preparations, supplements or;
- Testosterone derivatives;
- Topical corticosteroids on the upper arms and shoulders (e.g., hydrocortisone);
- Clomiphene;
- TRT from a source outside the study

5.4 Prior and Concomitant Therapy

Any prescription medications (antihypertensive medications in particular) and OTC aspirin, iron, folate, B12, vitamin D and calcium that the subject is receiving within 2 weeks prior to enrollment or receives during the study, must be recorded. Such medications will be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency. Other non-prescription medications should be recorded as a result of an AESI, AE leading to study drug discontinuation, or SAEs.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with AndroGel 1.62% can be located in the AndroGel 1.62% product label.

Subjects must be able to safely discontinue any prohibited medications 5 half-lives or 4 weeks prior to initial study drug administration. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

5.5 Withdrawal of Subjects and Discontinuation of Study

Every effort will be made to ensure that subjects continue to return to the clinic for study visits and avoid lost to follow-up (LTFU) during the conduct of the study. After the first missed visit, subjects that are potentially LTFU should receive a minimum of 3 phone calls, faxes, and or emails as well as one registered/certified mail letter. All attempts should be documented in the subject's source documentation.

A subject may voluntarily withdraw or be withdrawn from the study drug at any time for reasons including, but not limited to, the following:

- Confirmed serum T levels > 750 ng/dL even after down-titration to the lowest dose during the study;
- Confirmed repeat PSA > 4.0 ng/mL for men not taking 5 alpha-reductase inhibitors and PSA > 2.0 ng/mL for men taking 5-ARI during the study;
- Confirmed repeat Hct value > 54% during the study;

- Confirmed prostate or breast cancer diagnosis during the study;
- Any AE that in the investigator's opinion may affect the subject's safety.

Subjects who discontinue study drug with < 16 weeks of treatment may be replaced (see Section 7.7) and should follow the premature discontinuation procedures (Appendix D).

Discontinuation of Entire Study

AbbVie may terminate this study prematurely in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie, or its designee, will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

When the study ends or is terminated, all enrolled subjects continuing in the study will return for the FV procedures as specified in Appendix D, Study Activities. For subjects remaining on study drug at such a time, the post therapy SAE collection period will continue for 30 days following the termination of study drug therapy.

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

If a subject prematurely discontinues from study drug with < 16 weeks of treatment, he should not undergo the EOT procedures of ABPM and serial PK sampling, as he is not eligible for the per protocol analysis set.

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation Visit should be completed as soon as possible, preferably within 7 days of last dose of study drug. In addition, if a subject is willing, a 30-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs/SAEs have been resolved.

5.7 Study Drug

AndroGel 1.62% will be applied topically once daily in the morning beginning at the Day 1 Visit after confirmed valid ABPM assessment and should be applied at approximately the same time each day after that during the study. The starting dose of AndroGel 1.62% is 40.5 mg of T (2 pump actuations, applied to the upper arms and shoulders). It should not be administered to other parts of the body, including abdomen, genitals, chest, armpits (axillae), or knees.

AndroGel 1.62% can be dose adjusted between a minimum of 20.25 mg of T (1 pump actuation) and a maximum of 81.0 mg of T (4 pump actuations). For the first study drug administration at the Day 1 Visit,

and also at Week 2, Week 4, Week 16 ABPM, and End of Treatment Visits the subjects should apply the study drug while on site so that the site staff can observe the proper administration of study drug.

If subjects forget to apply their AndroGel 1.62% dose at their regularly scheduled dosing time, they should take the next dose at the next dosing time.

Subjects will be instructed to return all used and unused pump bottles to the study site staff at each study visit (see Operations Manual, Appendix E).

AbbVie will supply the AndroGel 1.62% as study drug. AbbVie provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie.

AndroGel 1.62% will be packaged in pump bottles with quantities sufficient to accommodate study design. Before using a new pump of study drug, the pump will need to be primed by pushing the actuator all the way down 3 times. The pump only needs to be primed when using a new pump for the first time.

Each pump bottle will be labeled per US requirements and the label must remain affixed to the pump bottle. Each pump bottle will contain a unique pump bottle kit number. This pump bottle kit number is assigned to a subject via IRT and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Study staff will fill in all pump bottle labels before dispensing to subjects. Study drug will only be used for the conduct of this study.

Controlled Substance Requirements

The investigator must agree to comply with all applicable Drug Enforcement Agency (DEA) laws and regulations regarding controlled substances as outlined in 21 CFR 1300. Additionally, the investigator must agree to limit access to the study drug only to the named Sub-investigators or to other appropriately designated study staff or monitoring personnel. Study drug will only be dispensed to subjects enrolled in the study by the investigator designee.

Study drug will only be shipped once the DEA license has been received from each site. The study drug must be shipped to the address listed on the Form DEA-223. Study drug must be securely stored at the same location according to DEA guidelines for CIII controlled substances. Upon receipt of a shipment, the investigator or designated study staff at the site will:

1. Open and inspect the shipment;
2. Verify the study drug supplies have been received intact, in the correct amounts and at the correct address;
3. Acknowledge receipt of study drug consignment via the IRT system.

5.8 Randomization/Drug Assignment

This is a single-arm open-label study; therefore, there will not be a randomization to treatment assignment. All subjects will be assigned a unique identification number by the IRT at SV1. For subjects who rescreen, the screening number assigned by the IRT at the SV1 should be used.

Subjects will be categorized in IRT by ongoing medical history of hypertension (Yes/No) at Baseline to ensure that 35% to 50% of subjects with an ongoing medical history of hypertension are enrolled.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified), the investigator is responsible for notifying IRB, regulatory authorities (as applicable), and AbbVie.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of AndroGel 1.62% product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events: Study Drug

An adverse event (AE) is defined as any untoward medical occurrence in a subject 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 unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or

accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

The investigator will monitor each subject on a routine basis throughout the study for clinical and laboratory evidence of SAEs, AESI, AEs leading to study drug discontinuation, and study procedure-related AEs. Any SAEs, AESI, AEs leading to study drug discontinuation, and study procedure-related AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded. All SAEs, AESI, AEs leading to study drug discontinuation, and study procedure-related AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as a SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.2 of the Operations Manual for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life

Outcome	threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event.

All SAEs, AESI, AEs leading to study drug discontinuation will be recorded from the time of study drug administration until the end of the study/study completion. Study procedure-related non-serious AEs and SAEs will be collected from the time the subject signs the study-specific informed consent until 30 days after the last dose of study drug. All SAEs, AESI, AEs leading to study drug discontinuation, and study procedure–related AEs or SAEs will be followed until resolution or achievement of a new stable state, until the subject withdraws consent for study participation, or until the final study-related communication (e.g., phone call at the end of the study or final study communication in subjects truly considered LTFU, whichever occurs first).

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the AndroGel 1.62% product in accordance with global and local requirements.

The only AEs to be collected in the study are those that meet the definition of an AESI, resulted in study discontinuation, study procedure-related AEs, or meet the regulatory criteria for an SAE. For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate case report form (CRF) page.

Adverse Events of Special Interest

The following AESI will be collected during the study:

- Hypertension

Adverse Event Severity and Relationship to Study Drug

The investigator will use the following definitions to rate the severity of each AE:

Mild	The AE is transient and easily tolerated by the subject.
Moderate	The AE causes the subject discomfort and interrupts the subject's usual activities.
Severe	The AE causes considerable interference with the subject's usual activities and may be incapacitating or life threatening.

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there

	is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

Pregnancy

Pregnancy of the subject's female partner will be reported to AbbVie within 24 hours of the site becoming aware of the pregnancy. Information regarding pregnancies in the partners of study subjects will be collected from the date of first dose through 30 days following the last dose of study drug. Information regarding a pregnancy occurrence in a study subject's partner and the outcome of the pregnancy will be collected. In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate informed consent for this purpose.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods in the protocol focus on the primary endpoint analysis. Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP).

7.2 Definition for Analysis Populations

The Full Analysis Set (FAS) includes all subjects who received at least 1 dose of study drug. The FAS will be used for baseline analyses and certain sensitivity analyses.

The per protocol population includes all subjects who received at least 1 dose of study drug, are at least 85% compliant to study drug, and have valid Baseline and EOT systolic ABP data. The per protocol population will be used for all analyses on endpoints based on 24-hour recording from ABPM device, including the primary endpoint, except for certain sensitivity analyses of the primary endpoint.

The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug. The Safety Analysis Set will be used for all other safety analyses not related to 24-hour collection from ABPM device.

7.3 Statistical Analyses for Efficacy

Efficacy will not be evaluated in this study.

7.4 Statistical Analyses for Safety

Primary Safety Endpoint

For the primary analysis, the primary endpoint of change from Baseline to EOT in average 24-hour SBP will be evaluated using a linear regression model with average 24-hour SBP at EOT as the outcome, and baseline average 24-hour SBP and pooled study center as covariates in the per-protocol population. If the upper confidence limit of the 1-sided 97.5% confidence interval (CI) of the estimate of the change from Baseline to EOT in average 24-hour SBP from the linear regression model is less than 3 mmHg, this will establish that the SBP at EOT is not greater than Baseline with a noninferiority margin of 3 mmHg.

Sensitivity analyses examining missingness of some SBP results during the 24-hour ABPM collections and impact of this missingness on the primary endpoint will be documented in the SAP.

Other Safety Endpoints

The continuous endpoints (e.g., change from Baseline to EOT in average daytime MAP, SBP, DBP, PP, and HR) will be summarized by mean, SD, minimum, and maximum. The categorical endpoints (e.g., subjects with new concomitant antihypertensive medications) will be summarized with n and percentage.

The following additional analysis will be performed:

- Graphical display of hourly ABPM averages that include SD bars for both SBP and DBP at the Baseline and EOT Visits.
- Cumulative distribution curves of 24-hour average SBP and DBP at the Baseline and EOT Visits.
- Forest plots of daytime, nighttime, and 24-hour average change from Baseline to EOT with 95% CI displays for SBP and DBP.

Subgroup Analysis of Safety Endpoints

All the analysis for the primary and other safety endpoints (except the sensitivity analyses of the primary endpoint) will be provided by the following subgroups based on history of hypertension:

- Subjects without an ongoing medical history of hypertension and without any antihypertensive medication(s) at Baseline;
- Subjects with an ongoing medical history of hypertension with any antihypertensive medication(s) at Baseline;
- Subjects with an ongoing medical history of hypertension without any antihypertensive medication(s) at Baseline.

Adverse Events

Treatment emergent AESI, AEs leading to study drug discontinuation and SAEs will be summarized in descending order of overall frequency by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT), as well as in a lexicographic order by system organ class (SOC) and MedDRA PT.

Treatment emergent AESI and SAEs will also be summarized according to their relationship to study drug and their maximum severity. In addition, treatment emergent AEs/SAEs that lead to study drug discontinuation will also be summarized.

Clinical Laboratory Data

Continuous summaries of mean changes from Baseline to each applicable visit for items such as PSA, lipids, Hct and hemoglobin will be summarized.

Vital Signs

Continuous summaries of the mean change from Baseline to each applicable visit in vital signs will be provided. Vital sign variables include, but are not limited to, SBP and DBP by office BP measurement, HR, respiratory rate (RR), and oral body temperature.

7.5 Interim Analysis

An analysis to estimate the SD of the change from Baseline to EOT in average SBP from 24-hour recordings will be conducted in a blinded fashion when approximately 70% of the planned subjects in the per protocol population (i.e., 120 subjects) have completed the EOT Visit. The objective of analysis is to re-estimate sample size if needed. A study database snapshot will be performed for this analysis. The sample size will be re-estimated with updated assumption of SD if necessary. The blinded sample size re-estimation (BSSR) analysis will be performed by an AbbVie statistician external to the study team who has access to unmasked ABPM data.

An interim database lock will be performed to unmask the Week 16 ABPM data after the last subject completes a valid EOT ABPM 24-hour collection or prematurely discontinues from the study.

7.6 Overall Type I Error Control

This study has one primary endpoint for which non-inferiority is tested, so no adjustment for multiple endpoints is needed. Analytically and through simulations, it has been shown that BSSR procedures (Section 7.7) do not meaningfully affect Type I error rate.[53] Therefore, no multiplicity adjustment is planned for the BSSR analysis.

7.7 Sample Size Determination

A sample size of 171 subjects will provide 90% power for a paired t-test with 0.025 one-sided significance level to show that the EOT average 24-hour SBP is not greater than the Baseline average 24-hour SBP with a non-inferiority margin of 3 mmHg, assuming the mean difference between EOT and

Baseline is an increase of 0.5 mmHg and the SD of the difference is 10 mmHg. The paired t-test is a good approximation of the power for the primary analysis using linear regression with covariate adjustment. Assuming a 10% loss of subjects from the per protocol population due to premature discontinuation, invalid ABPM at the Baseline or EOT Visit, or non-adherence to study drug, approximately 190 subjects will be enrolled to reach a minimum of 171 subjects who are at least 85% compliant to study drug and have valid ABPM data from Baseline and the EOT Visits.

If the dropout, non-evaluable ABPM, or non-adherence rates are higher than expected, enrollment will continue until the required number of evaluable subjects in the per protocol population is reached. If the SD is higher than the expected SD, an evaluation will be made to adjust the number of evaluable subjects if necessary.

Blinded Sample Size Re-Estimation

With a sample size of 171 subjects in the per protocol population, the study is powered at 90% if the SD of change from Baseline to EOT in systolic ABP is 10 mmHg. In order to ensure the assumed SD is correct for the study, a review and estimate of the SD will be conducted when approximately 70% of the planned subjects in the per protocol population (i.e., 120 subjects) have completed the EOT Visit. It will be performed by an AbbVie statistician external to the study team who has access to the unmasked ABPM data. If the estimated SD is larger than 10 mmHg, the sample size may be increased according to prespecified procedure based on the estimated SD from the masked data. Since the study team is masked to the postbaseline ABPM data until the end of the Treatment Period of the last subject and only SD is used in the sample size re-estimation, no multiplicity adjustment is needed for the BSSR.

A cap on the re-estimated sample size will be incorporated to ensure a feasible sample size. The final recalculated sample size in the per protocol population will be greater than or equal to the initial sample size of 171 subjects and less than or equal to the limit of cap sample size.

The detailed BSSR plan will be documented in the SAP.

8 ETHICS

8.1 Institutional Review Board (IRB)

The protocol, informed consent, recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the informed consent will be IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that

have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s).

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The end-of-study is defined as the date of the last subject's last visit/last procedure/last phone call.

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ABP	ambulatory blood pressure
ABPM	ambulatory blood pressure monitoring
AE	adverse event
AESI	adverse events of special interest
AHA	American Heart Association
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
BSSR	blinded sample size re-estimation
CFR	Code of Federal Regulations
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	case report form
DBP	diastolic blood pressure
DEA	Drug Enforcement Agency
DHT	dihydrotestosterone
DRE	digital rectal exam
DVT	deep vein thrombosis
E2	estradiol
IEC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOS	End of Study
EOT	End of Treatment
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hct	hematocrit

HR	heart rate
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
LTFU	lost to follow-up
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
OTC	over-the-counter
PE	pulmonary embolism
PK	pharmacokinetics
PP	pulse pressure
PSA	prostate-specific antigen
PT	preferred term
QTcF	Fridericia-corrected QT interval
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
SV1	Screening Visit 1
SV2	Screening Visit 2
T	testosterone
TA	Therapeutic Area
TA MD	Therapeutic Area Medical Director
T_{max}	time to maximum observed concentration
TRT	testosterone replacement therapy
TXA	thromboxane
US	United States

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M19-161: 24-Hour Ambulatory Blood Pressure Monitoring Study in Hypogonadal Men Receiving Testosterone Replacement Therapy

Protocol Date: 26 August 2020

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation (ICH) GCP and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate IRB/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	Clinical Program Development Program Lead	Clinical Program Development
[redacted]	Executive Medical Director	General Medicine Clinical Development
[redacted]	Medical Director, TA MD	General Medicine Clinical Development
[redacted]	Senior Manager	Statistics
[redacted]	TA Statistician	Statistics
[redacted]	Study Project Manager	Clinical Program Development
[redacted]	Associate Director	Regulatory Affairs
[redacted]	Director	Clinical Pharmacology and Pharmacometrics
[redacted]	Medical Writer	Medical Writing

TA = Therapeutic Area; TA MD = Therapeutic Area Medical Director

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities the subject encounters. The individual activities are described in detail in the **Operations Manual.**

Visit Windows Baseline ABPM (+ 7 days) Week 2 (± 4 days) Week 4 (± 7 days) Week 10 (+ 7 days) Week 16 ABPM (+ 7 days) Follow-Up (± 7 days) *Visit timing based on time elapsed from the Day 1 Visit*	SV1	SV2	Baseline ABPM	Day 1	Week 2 - Titration	Week 4 - Titration	Week 10 - Phone Call	Week 16 ABPM	End of Treatment	Premature Discontinuation	Unscheduled	30-Day Follow-Up Call
INTERVIEWS												
Informed consent	✓											
Eligibility Criteria	✓	✓	✓									
Subject/medical/surgical/hypertension history	✓		✓									
Alcohol and Nicotine Use	✓											
Adverse Event Assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/Concomitant Medication Assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Phone Call							✓					✓
EXAM												
Height, weight, and BMI		✓										
Vital signs (include oral temperature, HR and RR)	✓	✓	✓					✓	✓	✓	✓	
Office blood pressure measurements (cuff)	✓	✓	✓		✓	✓		✓		✓	✓	
Physical examination (full)		✓										
Physical examination (symptom directed)			✓					✓	✓	✓	✓	
Digital Rectal Exam		✓										
12-Lead ECG (after 5 minutes of supine rest)		✓										
Cuff size measurement	✓		✓					✓			✓	
Dispense/Collect ABPM device			✓	✓				✓	✓		✓	
Pre-ABPM Assessment			✓					✓			✓	
ABPM (24-hour collection)			✓					✓			✓	
ABPM Assessment (validity confirmation of ABPM collection)				✓					✓			

Visit Windows Baseline ABPM (+ 7 days) Week 2 (± 4 days) Week 4 (± 7 days) Week 10 (+ 7 days) Week 16 ABPM (+ 7 days) Follow-Up (± 7 days) *Visit timing based on time elapsed from the Day 1 Visit*	SV1	SV2	Baseline ABPM	Day 1	Week 2 - Titration	Week 4 - Titration	Week 10 - Phone Call	Week 16 ABPM	End of Treatment	Premature Discontinuation	Unscheduled	30-Day Follow-Up Call
CENTRAL LABS												
Testosterone	✓	✓		✓	✓	✓				✓		
Dihydrotestosterone (DHT)				✓					✓	✓		
Estradiol (E2)				✓					✓	✓		
Prostate-specific antigen (PSA)		✓							✓	✓	✓	
Hematocrit											✓	
Hematology (without differential)		✓							✓	✓		
Hemoglobin A1c		✓										
Chemistry (including serum creatinine for eGFR assessment by CKD-EPI equation at SV2 only)		✓							✓	✓		
Urinalysis (without microscopy)		✓										
Serial PK blood samples following ABPM assessment obtained at 0, 2, 4, and 6 - 8 hours									✓			
TREATMENT												
Enrollment			✓									
Subject applies study drug on site				✓	✓	✓		✓	✓			
Dispense study Drug				✓	✓	✓						
Collect Study Drug					✓	✓			✓	✓		
Study Drug Adherence Check					✓	✓			✓	✓		

ABPM = ambulatory blood pressure monitoring; BMI = body mass index; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HR = heart rate; PK = pharmacokinetics; RR = respiratory rate; SV1 = Screening Visit 1; SV2 = Screening Visit 2

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	20 November 2019
Version 2.0	19 February 2020

The purpose of this version (Version 3.0) is to change the lower limit of the DBP range from 70 mmHg to 60 mmHg in criterion number 5 (Section 5.1). **Rationale:** This was to optimize the DBP range.

The purpose of Version 2.0 was to correct minor clerical errors for consistency throughout the protocol and to clarify information in addition to the following:

Eligibility criterion number 4 (Section 5.1) was corrected to indicate that PSA values must be ≤ 3.0 ng/dL in men treated with 5-alpha reductase inhibitors. **Rationale:** This was to correct < 3.0 ng/dL.

A more detailed description of what constitutes an AE was added to Section 6.1. **Rationale:** Clarification of AE definition, including worsening of pre-existing conditions.

The statistical analysis of the primary endpoint was described in greater detail, and sensitivity analyses were added to Section 7.4. **Rationale:** Clarification.

In the Operations Manual Section 6.2, it was specified that the study monitor is to return unused study drug to the depot for destruction. **Rationale:** This was to clarify that sites are not to destroy study drug on site.

In the Operations Manual Section 6.4 clarifies the titration notifications. Reference to the IRT was removed, as the IRT is not used for dosing titration notification. **Rationale:** Clarification.

APPENDIX F. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M19-161

24-Hour ABPM in Hypogonadal Men on TRT

SPONSOR:	AbbVie Inc.	ABBVIE INVESTIGATIONAL PRODUCT:	AndroGel 1.62%

FULL TITLE: 24-Hour Ambulatory Blood Pressure Monitoring Study in Hypogonadal Men Receiving Testosterone Replacement Therapy

1 CONTACTS

Sponsor/ Emergency Medical Contact	[redacted], MD, MS AbbVie Inc. [redacted] 1 North Waukegan Road North Chicago, IL 60064 **EMERGENCY 24-hour Number:** **+1 (973) 784-6402**	Office: Mobile: Fax: Email: [redacted]
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SAE Reporting outside of RAVE	Email: PPDINDPharmacovigilance@abbvie.com	Fax: +1 (847) 938-0660
Protocol Deviations and Product complaints	[redacted] Study Project Manager [redacted] AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064	Phone: Mobile: Email: [redacted]
Certified Clinical Lab	Covance CLS 8211 SciCor Drive Indianapolis, IN 46214	Phone: + 1 (317) 273-7872 Fax: +1 (317) 616-4572
ABPM Lab	Bioclinica 211 Carnegie Center Drive Princeton, NJ 08540	Phone: +1 (877) 632-9432 Fax: +1 (609) 936-2602

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2 PROTOCOL ACTIVITIES BY VISIT

2.1 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Study Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 3.

SCREENING VISIT 1:

INTERVIEW	• Informed consent • Eligibility criteria evaluation[a] • Subject medical/surgical/ hypertension history • Alcohol and nicotine use	• Prior and concomitant medication assessment • AE assessment
EXAM	• Vital signs (include oral temperature, HR, and RR) • Office BP[b]	• Cuff size measurement
CENTRAL LAB	• Testosterone[c]	

AE = adverse event; BP = blood pressure; HR = heart rate; RR = respiratory rate; SV1 = Screening Visit 1; T = testosterone

a. The presence of hypogonadism symptoms must be confirmed prior to performing other SV1 activities.

b. The office BP measurement at SV1 (BP < 140/90 mmHg and > 100/60 mmHg) will be used to establish study eligibility (see Section 3.8). BP eligibility must be confirmed prior to collection of the serum T level sample.

c. Screening serum T level sample will be collected between 05:00 – 11:00. The blood sample draw at SV1 for serum T level must be confirmed as < 300 ng/dL or subject is a screen failure.

SCREENING VISIT 2:

INTERVIEW	• Eligibility criteria evaluation[a] • Concomitant medication assessment	• AE assessment
EXAM	• Vital signs (include oral temperature, HR, and RR) • Office BP[a] • Physical examination (full) • Height, weight and BMI[b]	• Digital rectal exam (DRE) • 12-lead ECG[c]
CENTRAL LAB	• Testosterone[d,e] • PSA • Hematology (without differential) • Hemoglobin A1c	• Chemistry (including serum creatinine for estimated glomerular filtration rate assessment using CKD-EPI equation) • Urinalysis (without microscopy)

AE = adverse event; BMI = body mass index; BP = blood pressure; CKD = chronic kidney disease; ECG = electrocardiogram; HR = heart rate; PSA = prostate-specific antigen; RR = respiratory rate; SV2 = Screening Visit 2; T = testosterone

a. The office BP measurement at SV2 (BP < 140/90 mmHg and > 100/60 mmHg) will be used to further establish study eligibility.

b. Height and weight will only be collected at SV2 to calculate BMI.

c. After 5 minutes of rest while supine.

d. Beginning at SV2, the serum T level sample should be drawn fasting. Screening serum T level sample will be collected between 05:00 – 11:00.

e. The blood sample draw at SV2 for serum T level must be confirmed as < 300 ng/dL for study eligibility consideration.

BASELINE ABPM:

INTERVIEW	• Eligibility criteria evaluation[a] • Concomitant medication assessment[b] • Subject medical/surgical/ hypertension history	• AE assessment
EXAM	• Pre-ABPM assessment[a] • Vital signs (include oral temperature, HR, and RR)[a] • Office BP[a] • Physical examination (symptom directed)[a]	• Cuff size measurement • Dispense ABPM device • Start ABPM 24-hour collection[c]
TREATMENT	• Enrollment	

ABPM = ambulatory blood pressure monitoring; AE = adverse event; BP = blood pressure; HR = heart rate; RR = respiratory rate

a. The pre-ABPM assessment is part of the eligibility criteria evaluation and should be conducted along with vital signs (including office BP measurements) and, only if needed, a symptom-directed physical examination prior to performing any other study activities. This assessment is an evaluation whether subject is fit for the start of ABPM 24-hour collection. If the subject exhibits clinical symptoms of an acute illness, the Baseline ABPM Visit should be rescheduled to occur within 7 days.

b. If subject is managing hypertension with any antihypertensive medication(s), the subject should be instructed to bring the medication(s) to the site and take the medication dose(s) while on site.

c. The site will place the ABPM device on the subject (to be performed between 06:00 – 11:00). The site will record the start time of ABPM 24-hour collection.

DAY 1:

INTERVIEW	• Concomitant medication assessment[a]	• AE assessment
EXAM	• ABPM assessment[b,c]	• Collect (and dispense if repeat collection needed) ABPM device[c,d]
CENTRAL LAB	• Testosterone[d] • DHT[d]	• Estradiol (E2)[d]
TREATMENT	• Dispense study drug	• Subject applies study drug on site[c,e]

ABPM = ambulatory blood pressure monitoring; AE = adverse event;
DHT = dihydrotestosterone; HR = heart rate; RR = respiratory rate; T = testosterone

a. If subject is managing hypertension with any antihypertensive medication(s), the subject should be instructed to bring the medication(s) to the site and take the medication dose(s) while on site.

b. ABPM assessment (validity confirmation of ABPM 24-hour collection) should be conducted prior to performing Day 1 study activities, which include collection of lab samples (T, DHT, and E2) and study drug administration/subject on-site study drug application.

c. The time of ABPM 24-hour collection completion and subject on-site study drug application will be recorded by site.

d. If the Baseline ABPM 24-hour collection is invalid, a repeat Baseline ABPM 24-hour collection (Unscheduled Visit) will be required and should be performed within 7 days. ABPM assessment (validity confirmation of repeat ABPM 24-hour collection) must be confirmed prior to collection of lab samples and study drug dispensation/subject on-site study drug application.

e. The first dose of study drug will be applied by subject while on site after all other Day 1 Visit procedures (including blood draw) are completed and only after a valid ABPM assessment has been confirmed. The site will record the time of on-site study drug application.

WEEK 2:

INTERVIEW	• Concomitant medication assessment[a]	• AE assessment
EXAM	• Office BP	
CENTRAL LAB	• Testosterone (for titration)	
TREATMENT	• Collect study drug • Dispense study drug	• Study drug adherence check • Subject applies study drug on site[b]

AE = adverse event; BP = blood pressure; T = testosterone

a. If subject is managing hypertension with any antihypertensive medication(s), the subject should be instructed to bring the medication(s) to the site and take the medication dose(s) while on site.

b. Subject should be instructed to bring study drug to the site. Study drug dose from the newly dispensed study drug will be applied by subject while on site at Week 2 Visit after the T blood draw.

WEEK 4:[a]

INTERVIEW	• Concomitant medication assessment[b]	• AE assessment
EXAM	• Office BP	
CENTRAL LAB	• Testosterone (for titration)	
TREATMENT	• Collect study drug • Dispense study drug	• Study drug adherence check • Subject applies study drug on site[c]

AE = adverse event; BP = blood pressure; T = testosterone

a. The Week 4 Visit should be scheduled no sooner than 10 days after the Week 2 Visit to allow for results from the T titration collection at the Week 2 Visit.

b. If subject is managing hypertension with any antihypertensive medication(s), the subject should be instructed to bring the medication(s) to the site and take the medication dose(s) while on site.

c. Subject should be instructed to bring study drug to the site. Study drug dose from the newly dispensed study drug will be applied by subject while on site at Week 4 Visit after the T blood draw.

WEEK 10 (PHONE CALL ONLY):

INTERVIEW	• Concomitant medication assessment	• AE assessment

AE = adverse event

WEEK 16, ABPM VISIT

INTERVIEW	• Concomitant medication assessment[a]	• AE assessment
EXAM	• Pre-ABPM assessment[b] • Vital signs (include oral temperature, HR, and RR)[b] • Office BP[a] • Physical examination (symptom directed)[a]	• Cuff size measurement • Dispense ABPM device[e] • Start ABPM 24-hour collection[d]
TREATMENT	• Subject applies study drug on site[c,d]	

ABPM = ambulatory blood pressure monitoring; AE = adverse event; BP = blood pressure; HR = heart rate; RR = respiratory rate

a. If subject is managing hypertension with any antihypertensive medication(s), the subject should be instructed to bring the medication(s) to the site and take the medication dose(s) while on site.

b. The pre-ABPM assessment should be conducted along with vital signs (including office BP measurements) and, only if needed, a symptom-directed physical examination prior to any other study activities. This assessment is an evaluation whether subject is fit for the start of ABPM 24-hour collection. If the subject exhibits clinical symptoms of an acute illness, the Week 16 ABPM Visit should be rescheduled to occur within 7 days.

c. Subject should be instructed to bring study drug to the site. Study drug will be applied by the subject while on site before the site places the ABPM device on the subject.

d. The site will place the ABPM device on the subject (to be performed between 06:00 – 11:00). The site will record the start time of ABPM 24-hour collection and the time of on-site study drug application.

e. Every effort will be made by site to dispense the same ABPM device that subject used at the Baseline ABPM Visit.

END OF TREATMENT:

INTERVIEW	• Concomitant medication assessment[a]	• AE assessment
EXAM	• ABPM assessment[b,c] • Vital signs (include oral temperature, HR, and RR) • Physical examination (symptom directed)	• Collect (and dispense if repeat collection needed) ABPM device[d]
CENTRAL LAB	• DHT[b] • Estradiol (E2)[b] • PSA[b] • Hematology (without differential)[b]	• Chemistry (no serum creatinine)[b] • Serial PK blood samples[b,e]
TREATMENT	• Collect study drug[f]	• Study drug adherence check[f] • Subject applies study drug on site[c]

ABPM = ambulatory blood pressure monitoring; AE = adverse event;
DHT = dihydrotestosterone; EOT = End of Treatment; HR = heart rate; PK = pharmacokinetics;
PSA = prostate-specific antigen; RR = respiratory rate

a. If subject is managing hypertension with any antihypertensive medication(s), the subject should be instructed to bring the medication(s) to the site and take the medication dose(s) while on site.

b. ABPM assessment (validity confirmation of ABPM 24-hour collection) should be conducted prior to performing EOT study activities, which include collection of lab samples and serial PK blood samples.

c. Subject should be instructed to bring study drug to the site. The site will record time of on-site study drug application and time of the Week 16 ABPM 24-hour collection completion.

d. If the Week 16 ABPM 24-hour collection is invalid, a repeat Week 16 ABPM 24-hour collection (Unscheduled visit) will be required and should be performed within 7 days, and the rest of the EOT procedures should not be performed until after the next ABPM assessment.

e. Serial PK blood samples (4 samples in total) to be collected at 0 hour (immediately prior to subject on-site application of study drug), with an allowance of + 10-minute window), and at 2 hours ± 5 minutes, 4 hours ± 5 minutes, and between 6 to 8 hours following study drug application and only after ABPM assessment (validity confirmation of Week 16 ABPM 24-hour collection).

f. Completion of a valid Week 16 or repeat Week 16 ABPM 24-hour collection must occur prior to the study drug adherence check and collection of study drug.

PREMATURE DISCONTINUATION:

INTERVIEW	• Concomitant medication assessment	• AE assessment
EXAM	• Vital signs (include oral temperature, HR, and RR) • Office BP	• Physical examination (symptom directed)
CENTRAL LAB	• Testosterone • DHT • Estradiol (E2)	• PSA • Hematology (without differential) • Chemistry (no serum creatinine)
TREATMENT	• Collect study drug	• Study drug adherence check

AE = adverse event; BP = blood pressure; DHT = dihydrotestosterone; HR = heart rate; PSA = prostate-specific antigen; RR = respiratory rate

UNSCHEDULED:

INTERVIEW	• Concomitant medication assessment[a]	• AE assessment
EXAM	• Pre-ABPM assessment[b,e] • Vital signs (include oral temperature, HR, and RR)[b] • Office BP[b] • Physical examination (symptom directed)[b]	• Cuff size measurement[e] • Dispense ABPM device[c,e] • Start ABPM 24-hour collection[d,e]
CENTRAL LAB	• Hematocrit[d]	• PSA[d]
TREATMENT	• Subject applies study drug on site[c]	

ABPM = ambulatory blood pressure monitoring; AE = adverse event; BP = blood pressure; HR = heart rate; PSA = prostate-specific antigen; RR = respiratory rate

a. If subject is managing hypertension with any antihypertensive medication(s), the subject should be instructed to bring the medication(s) to the site and take the medication dose(s) while on site.

b. When an Unscheduled Visit is required for a repeat ABPM 24-hour collection, a Pre-ABPM assessment should be conducted along with vital signs (including office BP measurements) and only if needed, a symptom-directed physical examination prior to any other study activities. This assessment is an evaluation whether subject is fit for the start of ABPM 24-hour collection. If the subject exhibits clinical symptoms of an acute illness, a new Unscheduled Visit should be rescheduled to occur within 7 days.

c. When an Unscheduled Visit is required for a repeat ABPM 24-hour collection, every effort will be made by site to dispense the same ABPM device that the subject used at the Baseline ABPM Visit. If the repeat ABPM is for Week 16, the subject should be instructed to bring study drug to the site. Study drug will be applied by the subject while on site before the site places the ABPM device on the subject. The site will place the ABPM device on the subject (to be performed between 06:00 – 11:00). The site will record the start time of ABPM 24-hour collection and time of on-site study drug application.

d. These tests may be performed at the Unscheduled Visit only if deemed necessary by the investigator.

e. Applicable to repeat ABPM 24-hour collection.

2.2 Individual Post-Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Post-Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about the activities is presented in Section 3.

30-DAY FOLLOW-UP (PHONE CALL ONLY): 

INTERVIEW	• Concomitant medication assessment	• AE assessment

AE = adverse event

3 STUDY PROCEDURES

3.1 Study Subject Information and Informed Consent

The investigator or designee will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject or any medications being discontinued by the subject in order to participate in this study, the informed consent form will be reviewed, signed, and dated by the subject or their legally authorized representative, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding potential benefits for subjects, potential risks to subjects, and for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

3.2 Medical History

For all subjects, a complete medical, surgical and hypertension history will be obtained at the Screening visit, as specified in Section 2.1. In addition, demographics and history of alcohol and nicotine use will be obtained from each subject during the Screening Period. The subject's medical history will be updated at the Baseline ambulatory blood pressure monitoring (ABPM) Visit. This updated medical/surgical history will serve as the baseline for clinical assessment.

3.3 Concomitant Medications

All concomitant medications along with their dosage and indications will be documented throughout the study. Any change in antihypertensive medication(s) will be documented throughout the study, including start of new medications or dose increase of existing medication(s) reported by the subject at Screening.

At the visits as specified in Section 2.1, if the subject is managing hypertension with any antihypertensive medication(s), the subject should be instructed to bring the medication(s) to the site and take the medication dose(s) while on site.

3.4 Adverse Event Assessment

Please refer to Section 4.1.

3.5 Pharmacokinetic Sampling

Blood samples for analysis of testosterone (T) will be collected at time points specified in Section 2.1.

Additional information on the collection, handling/processing, disposition, and measurement methods can be found in the lab manual.

3.6 12-Lead Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at the designated study visit as specified in Section 2.1.

The ECG should be performed prior to blood collection and after the subject has rested in a supine position for approximately 5 minutes.

The ECG will be interpreted by an appropriately qualified physician at the site ("local reader"). The local reader from the site will sign and date all ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source documents. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected.

Electrocardiogram with QT interval corrected for HR using Fridericia-corrected QT interval (QTcF) should be reported (or calculated) and documented in the source documents and later transcribed on to the appropriate electronic case report form (eCRF), if QTcF prolongation is observed (> 430 msec). In addition, any clinically significant findings will be documented in the source documents and later transcribed on to the appropriate eCRF. Each signed original ECG may be reviewed by the responsible site monitor and kept with subject's source documents on site.

If there are clinically significant findings, the investigator must contact the AbbVie TA MD before enrolling the subject. The subject may have a repeat ECG at any time during the study as warranted based on the investigator's opinion.

3.7 Height and BMI, Weight

Height and weight will be measured at SV2 only for calculation of body mass index (BMI); the subject will not wear shoes. Body weight will be measured on a calibrated scale shortly after the subject empties his bladder. Subject should wear light indoor clothing with pockets empty and without shoes, belts, jewelry or other accessories. Weight may be recorded in kilogram (kg) to the nearest 0.1 kg or in pounds (lb) to the nearest 0.25 lb. If possible, the same scale should be used for all weight measurements.

Body mass index is defined as the subject weight in kilograms divided by the subject height in meters squared (kg/m^2) and should be calculated to the nearest one-tenth unit. The BMI calculation should be recorded in the Screening Visit source documents and case report form. The following formulas will be used to convert to metric units for calculation of BMI:

Pound (lb) ÷ 2.2 = Kilogram (kg)

Inch (in) × 0.0254 = Meter (m)

Body mass index calculations will be made by the investigator or designee during SV2 using the following formula:

Body mass index (kg/m^2) = weight (kg) ÷ [height (m) at Screening Visit]^2

3.8 Vital Signs

Vital sign determinations of HR, RR, and oral body temperature will be obtained at visits as specified in Section 2.1. Measurements should be assessed consistently throughout the study. Vital signs measurements determined at the Pre-ABPM assessment will serve as baseline.

Blood pressure (BP) and HR should be measured after the subject has been sitting for at least 5 minutes.

Measurements should be assessed consistently throughout the study.

Office BP Measurements

At SV1, subjects will be assessed for pre-existing hypertension based on medical history. At SV1 and SV2, subjects will be assessed for BP eligibility prior to T testing.

Blood pressure will be measured in both arms with an automated oscillometric device using a standardized measurement protocol according to the recommendations for indirect measurement of arterial BP of the AHA.[34]

See Section 7.2 for further details.

3.9 Physical Examination

A complete physical examination will be performed at SV2. The physical examination at SV2 will serve as the baseline physical examination for clinical assessment. All other physical examinations as indicated in Section 2.1 will be symptom-directed examinations.

Any significant physical examination findings not present at Baseline and detected on subsequent examinations will be documented and any significant findings will be reported. All findings will be captured on the appropriate eCRF page.

When deemed necessary by the investigator, a symptom-directed physical examination can be performed at the Unscheduled Visit.

Digital Rectal Examination (DRE)

A digital rectal exam (DRE) will be performed at SV2 and should be performed after the PSA blood draw. The DRE will not be required if the subject had a previous normal DRE within 6 months of SV1 and the written documentation of the DRE result is provided. An abnormal DRE necessitating further clinical work up will exclude the subject from the study until any prostatic abnormalities have been evaluated and deemed not exclusionary. An enlarged prostate on DRE due to Benign Prostatic Hyperplasia is not exclusionary.

3.10 Dispense Study Drug

The first dose of study drug will be applied by subject while on site after all other Day 1 Visit procedures are completed and only after a valid ABPM assessment has been confirmed. Thereafter, study drug will be dispensed at designated study visits during the Treatment Period. At the designated scheduled study visits, subjects will return to the site to obtain new supply of study drug and return used/unused study drug packaging supply. The unused study drug returned by the subject will not be re-dispensed. The investigator or designee will access the IRT system at each study visit prior to dispensing study drug to the subject. Study drug cannot be dispensed without using the IRT system. Study pump bottles will be labeled with their unique pump bottle kit number.

3.11 Clinical Laboratory Tests

The blood samples for serum chemistry tests (and sex steroids) will be collected following a minimum 8-hour fast (with exception of SV1, which may be non-fasting). At the Day 1 Visit, a fasting blood sample should be collected prior to the first dose of study drug. Blood samples should still be drawn if the subject did not fast for at least 8 hours. Fasting or non-fasting status will be recorded in the source documents and on the laboratory requisition. The laboratory test results from SV2 will serve as baseline for this study.

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests. Laboratory reference ranges will be obtained prior to the initiation of the study.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory.

If a laboratory test value is outside the reference range and the investigator considers the laboratory result to be clinically significant, the investigator will:

- repeat the test to verify the out-of-range value;
- follow the out-of-range value to a satisfactory clinical resolution; or
- discontinue the subject from the study or require the subject to receive treatment; in this case, the laboratory result will be recorded as a study-specific adverse event (AE) (See Section 6.1 of the protocol).

All Screening laboratory results must be reviewed, signed, and dated by the investigator or sub-investigator prior to enrollment. Subjects will not be enrolled into the study if laboratory or other Screening result abnormalities are deemed clinically significant by the investigator or sub-investigator.

Hematology	**Clinical Chemistry**[a]	**Urinalysis**[b]
Hematocrit Hemoglobin Red blood cell count White blood cell count Platelet count (estimate not acceptable) Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration	Blood urea nitrogen Creatinine[c] Total bilirubin Albumin Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase Gamma-glutamyl transferase Sodium Potassium Calcium Inorganic phosphate Uric acid Cholesterol Low-density lipoprotein cholesterol High-density lipoprotein cholesterol Total protein Glucose Triglycerides Bicarbonate/CO_2 Chloride	Specific gravity Ketones pH Protein Glucose Blood Leukocytes Nitrites
		Other Laboratory Tests
		Prostate specific antigen Hemoglobin A1c
		Sex Steroids[a]
		Testosterone[d] Dihydrotestosterone Estradiol
		PK Assay
		At EOT visit only: Serial PK blood samples following ABPM assessment obtained at 0, 2, 4, and 6 - 8 hours

ABPM = ambulatory blood pressure monitoring; EOT = End of Treatment; PK = pharmacokinetic; SV = Screening Visit

a. Minimum 8-hour fast except for SV1.

b. A dipstick urinalysis (without microscopy) will be completed by the central laboratory at SV2.

c. Serum creatinine will be collected at SV2 only and used to calculate eGFR (central laboratory performing calculations). An eGFR assessment (CKD-EPI Equation) will be performed.

d. Testosterone alone will be measured for eligibility at SV1 and SV2, and for titration at Weeks 2 and 4.

Clinical Chemistry

A minimum 8-hour fast will be necessary for blood samples to be drawn for chemistry. If a subject is not able to fast when necessary due to unforeseen circumstances, the non-fasting status will be recorded in subject source documentation.

Urinalysis

Dipstick urinalysis will be completed by the central laboratory at SV2. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis (only if needed) at the central laboratory.

Sex Steroids

Blood samples for serum T level, dihydrotestosterone (DHT), and estradiol (E2) will be collected at the visits as specified in Section 2.1. Testosterone samples obtained at the Weeks 2 and 4 Visits will be used for titration of the T study drug dose. For information on Screening serum T level, refer to the study inclusion criteria. After study enrollment, pre-dose serum T level samples will be collected at 24 hours (± 2 hours) of the last applied dose for the purpose of titration. For example, if the last applied dose was at 11:00 am the day prior to the study visit, the blood sample should be taken between 9:00 am to 1:00 pm. Subjects should not apply their regularly scheduled study drug dose prior to the in-person study visits as defined in Section 2.1. Subjects should receive a reminder to apply the dose 24 hours before the study visit, even if that is not their usual study drug application time.

The following subjects should be rescheduled within 1 week for a serum T level if their serum T cannot be drawn 24-hours (± 2 hours) from the last applied dose:

- Subjects who apply a dose less than 22 hours from the time of serum T sample collection.
- Subjects who apply a dose greater than 26 hours from the time of serum T sample collection.

Subjects should bring their current study drug to each on-site study visit. Subjects who forget to bring the study drug to their study visit should arrange to return study drug to study site as soon as possible. The dose applied during the study visit will come from the newly dispensed study drug.

Prostate-specific antigen

A blood draw to measure PSA should occur prior to the DRE as prostate manipulation can falsely elevate PSA. Only men who have a T < 300 ng/dL at SV1 will have a PSA evaluated from that same sample. At Screening, the PSA must be ≤ 3.0 ng/mL (≤ 1.5 ng/mL in men receiving 5-alpha reductase inhibitors).

3.12 Subject Withdrawal from Study

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the

investigator's best clinical judgment, irrespective of whether the subject decides to continue participation in the study.

3.13 Unscheduled Visits

An Unscheduled Visit may occur for a variety of reasons. During Unscheduled Visits, concomitant medication, AE assessments, vital signs (including office BP), and a symptom-directed physical examination (only if needed) should be performed. Blood and urine samples may be obtained for the laboratory tests listed in Section 3, or for other tests, at the investigator's discretion.

If a blood sample is collected for PSA or hematocrit at the Unscheduled Visit and there is an increase in absolute values as specified in Section 5.5 of the protocol, the increase should be confirmed by repeating the test. If the increase is confirmed after 2 blood draws, the subject should be discontinued from receiving study drug.

If an ABPM assessment requires a repeat due to device malfunction or confirmation of the invalid ABPM collection, the repeat ABPM 24-hour collection should be performed at the Unscheduled Visit. Study activities for the Unscheduled Visit are outlined in Section 2.1.

3.14 Ambulatory Blood Pressure Measurements

ABP measurements will be collected at the visits as specified in Section 2.1. Every effort should be made to use the same ABPM device for the Baseline and Week 16 ABPM for each individual subject. The start of each ABPM 24-hour collection is to be performed around the same time of day for each visit, between 06:00 – 11:00.

Study sites will be provided with a SpaceLabs ABP monitor from the cardiac safety core lab. The ABPM recordings will be transmitted to the core lab for centralized management of the data.

The ABP monitor will be set to automatically measure and record BP every 30 minutes for 24 hours. The inflation sequence for this protocol will be outlined in the ABPM training manual. The ABPM 24-hour collection will be conducted over a 2-day period. On the first day, the ABP monitoring device is fitted on the subject by the site; the subject leaves and then returns the following day for ABP monitor removal.

At the completion of each ABPM 24-hour collection, the ABPM data will be downloaded from the device to a laptop provided by the core lab. The ABPM data will be evaluated against a set of quality control criteria designed specifically for this study to define a valid monitoring. The quality control results will be immediately available for the clinical staff. If the quality criteria are not met, the investigator will ask the subject to return to the clinical site to repeat the ABPM 24-hour collection within 7 days. In this case, Day 1 Visit would follow completion of the repeat Baseline ABPM and the End of Treatment (EOT) Visit would follow completion of the repeat Week 16 ABPM. Repeat ABPM will be performed at an Unscheduled Visit.

A complete listing and definitions of the quality control criteria are outlined in the ABPM training manual.

Study sites will remain masked to the Week 16 ABPM data until the End of Treatment Period of the last subject; however, the site will be unmasked to the ABPM validity report. The investigator or designee will assess the validity of ABPM data based on the results that are immediately available on site once data is downloaded from the monitoring device, to the study configured laptop, utilizing ABPM specific software. PI or designee can then determine if a repeat ABPM 24-hour collection is required.

Sites will receive training on the use of the ABPM technology and software platform provided by the core lab. Additional information related to the ABPM procedures for the study will be provided in the ABPM Site Manual and ABPM Quick Reference Guide provided by the ABPM core lab.

The following ABPM procedures will be performed over a 2-day period:

First Day: Application

The BP cuff of the ABP monitor will be fitted, preferably on the subject's non-dominant arm, by designated study staff completing the clinic BP readings. The designated study site staff will use the 24-hour ABPM Application Worksheet provided by the core lab during the ABPM application process. Verification readings will be obtained prior to the beginning of test reading. The subject will be instructed regarding ABPM procedures and the ABPM Subject Instruction/Error Codes Handout provided by the core lab will be reviewed with the subject.

Second Day: Removal

The subject will return to the study site and the ABP monitor will be removed only after it has been worn for a minimum of 24 hours from the "Beginning of Test" reading. The ABPM data will be downloaded and quality control evaluated on site, using the study specific ABPM software. The quality control criteria for the specific monitoring will be immediately displayed on the ABPM laptop. If an ABPM 24-hour collection does not meet the study specific criteria ("fails"), the designated site staff should contact the ABPM core lab project team to review and determine if a repeat ABPM 24-hour collection is required for that specific ABPM Visit.

SpaceLabs System

The SpaceLabs 90217 ABP monitor is a small, light-weight unit with batteries, pouch, and strap and is designed to take up to 240 BP measurements (range: systolic 60 to 260 mmHg; diastolic 30 to 200; mean 40 to 230 mmHg) and HR measurements (range: 40 to 180 beats) for a 24- or 48-hour period. The monitor is carried in a pouch that may be worn on a waist-belt or on a shoulder strap. Blood pressure and HR measurements are taken oscillometrically, using a cuff, which is inflated twice hourly over a 24-hour period. Programming will allow the ABP monitor to specify the duration of the monitoring period, subject information to be incorporated in the analysis, the time format, the measurement interval, the presence or absence of the audible monitor tone during specified periods of the recording period (e.g., sleep), event code display and whether or not to display data on the digital display for reading by the subject.

Selection of Cuff Size for ABPM

Correct measurement of BP for ABPM requires the use of a cuff that is appropriate to the size of the non-dominant upper arm. The non-dominant arm will be preferred for consistency.

ABPM Procedures for Subject

The ABPM vendor (Bioclinica) will provide the site staff with access to electronic training modules and a Study Site Training Manual inclusive of subject instructions for use.

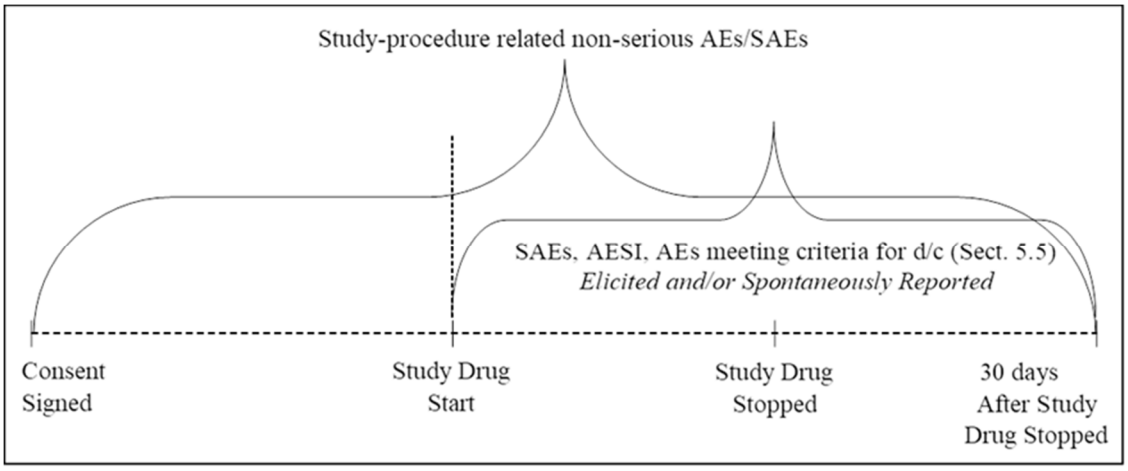
3.15 End of Study/Study Completion

The last visit/procedure/contact (e.g., office visit or phone call) with the subject will serve as the End of Study (EOS) for each subject. For subjects completing at least 16 weeks of treatment on study drug, there will be a follow up phone call in approximately 30 days. For subjects prematurely discontinuing study drug prior to Week 16/EOT, the follow up phone call at approximately 30 days after the last visit will serve as the EOS.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All SAEs, AESI, and AEs leading to study drug discontinuation, will be recorded from the time of study drug administration until the end of the study/study completion. Study procedure-related non-serious AEs and SAEs will be collected from the time the subject signs the study-specific informed consent until 30 days after the last dose of study drug. All SAEs, AESI, AEs leading to study drug discontinuation, and study procedure-related non-serious AEs or SAEs will be followed until resolution or achievement of a new stable state, until the subject withdraws consent for study participation, or until the final study-related communication (e.g., phone call at the end of the study or final study communication in subjects truly considered LTFU, whichever occurs first).



AE = adverse event; AESI = adverse event of special interest; d/c = discontinuation; SAE = serious adverse event

4.2 Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture/RAVE® system. Serious adverse event that occur prior to the site having access to the RAVE system, or if RAVE is not operable, should be documented on the SAE nonCRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: PPDINDPharmacovigilance@abbvie.com
FAX to: +1 (847) 938-0660

For safety concerns, contact the Men's and Women's Health Safety Team at:

Men's and Women's Health Safety Team
1 North Waukegan Road
North Chicago, Illinois 60064
Office: +1 (847) 935-7577
Email: GRPD_SafetyManagment_Hormones@abbvie.com

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
[redacted], **MD, MS**
AbbVie Inc.
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:

Office: [redacted]
Mobile:
Fax:
Email:

In emergency situations involving study subjects when the primary TA MD is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

HOTLINE: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product in accordance with Directive 2001/20/EC.

5 COUNTRY-SPECIFIC REQUIREMENTS

This section is not applicable, as this study does not have sites outside of the US.

6 STUDY DRUG

6.1 Treatments Administered

The study drug (AndroGel 1.62%) will be dispensed in the form of a topical gel at the visits listed in Section 2.1. Subjects will be instructed to take study drug at the same time every day. The first dose of study drug will be applied by subject while on site after all other Day 1 Visit procedures are completed and only after a valid ABPM 24-hour collection has been confirmed. Subject will be instructed to bring study drug in at Week 2, Week 4, Week 16 ABPM, and EOT Visits, and apply the study drug while on site.

Study drug must not be dispensed without contacting the IRT system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. At the end of the Treatment Period or at the Premature Discontinuation Visit, the site will contact the IRT system to provide visit date information and study drug return information for each kit.

6.2 Packaging and Labeling

The study drug will be supplied in a metered-dose pump, containing AndroGel 1.62%. Each actuation delivers 20.25 mg T.

Each pump bottle will be labeled per US requirement. Labels must remain affixed to the pump bottles. Site staff should fill in all pump bottle labels prior to dispensing to subject. The approximate dosage and duration for one bottle are depicted in Table 1.

Table 1. Approximate Dosage and Duration of Use for 1 Bottle of Study Drug

Dosage	Duration of Use for 1 Bottle
20.25 mg (1 actuation)	60 days
40.5 mg (2 actuations)	30 days
60.75 mg (3 actuations)	20 days
81.0 mg (4 actuations)	15 days

Storage and Disposition of Study Drug

Upon receipt, study drug should be stored as specified on the label and kept in a secure location:

- Store AndroGel 1.62% at 59°F to 86°F (15°C to 25°C);

- Keep AndroGel 1.62% away from fire;
- Keep AndroGel 1.62% and all medicines out of the reach of children.

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned by the study monitor to the depot for destruction.

6.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, single arm study. All eligible subjects will receive AndroGel 1.62%.

At SV1, all subjects will be assigned a unique identification number through the use of the IRT. For subjects who do not meet the study eligibility criteria, the site staff must contact the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number assigned at SV1 throughout the study. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Contact information and user guidelines for IRT use will be provided to each site.

6.4 Selection and Timing of Dose for Each Subject

The starting dose of AndroGel 1.62% is 40.5 mg of T (2 pump actuations, applied topically once daily in the morning). Based on serum T levels obtained at the Weeks 2 and 4 visits, subjects will be titrated up or down by 20.25 mg if their serum T levels are < 350 ng/dL or > 750 ng/dL, respectively. The final titrated doses will be 20.25 mg, 40.5 mg, 60.75 mg, or 81.0 mg, and subjects will remain on their final titrated dose following the Week 4 assessment until EOT.

Before using a new pump of study drug, the pump will need to be primed by pushing the actuator all the way down 3 times. Study drug dispensed while priming the pump should not be used. Subject should be instructed to dispose of it by washing it down the sink to avoid accidental exposure to others. The pump only needs to be primed when using a new pump for the first time.

Titration Instructions

Titration will be based on the predose morning total serum T concentrations. Subjects will return for predose serum T assessment 24 hours (± 2 hours) after the last applied dose according to the schedule in Section 2.1. Subjects will be asked when they last applied study drug. Subjects should be rescheduled within 1 week for a serum T level if their serum T cannot be drawn 24 hours (± 2 hours) from the last applied dose. Within approximately 7 days of these titration study visits, the subject's dose may be titrated up or down in 20.25 mg increments or remain on the previously assigned dose, based on prespecified criteria (Table 2). No dose can be titrated below 20.25 mg or above 81.0 mg during the course of the study.

Table 2. Dose Titrations

Pre-Dose (Preferably Morning) Sample Collection for Serum Testosterone Concentrations to Occur Within 24 Hours (± 2 hours) Following the Last Applied Dose	Dose Titration
Greater than 750 ng/dL	Decrease daily dose by 20.25 mg (one pump actuation)
Between 350 ng/dL and 750 ng/dL, inclusive	No change: continue on current dose
Less than 350 ng/dL	Increase daily dose by 20.25 mg (one pump actuation)

If the serum total T is > 750 ng/dL, the dose should be decreased by 1 actuation. If the serum total T is < 350 ng/dL, the dose should be increased by 1 actuation. If the serum total T is between 350 ng/dL and 750 ng/dL, inclusive, the dose should remain the same. The site staff will contact the subject (by phone, via email, etc.) and instruct the subject to reduce the dose by 1 study drug actuation, to increase by 1 study drug actuation, or to remain on the same dose of the study drug.

If the serum T is > 750 ng/dL even after down-titration to the lowest dose, the results should be confirmed by a repeat blood sample by the central laboratory. If the repeat total T is > 750 ng/dL, subject may need to be discontinued from study drug.

If subjects are instructed by site staff to titrate following Week 2 and Week 4 titration visits, they will be required to cross out the previous instructions on pump bottle label specifying their previous number(s) of pumps/actuations per day or dose and fill in their updated number of pumps/actuations per day or dose.

Should a subject's dose require titration, site personnel will communicate this to the subjects within approximately 3 days from the receipt of the lab results.

Study Drug Application Sites

For the first study drug administration at Day 1 Visit, the subject should administer the study drug while on site so that the site staff can observe the proper administration of study drug.

On subsequent study visit days, subjects should not apply their daily dose until after a sample is collected to measure serum T (See Section 2.1 for titration study visits). Following sample collection, subjects will apply study drug while on site. Subjects should be rescheduled within 1 week for a serum T level if their serum T cannot be drawn 24 hours (± 2 hours) from last applied dose (see Section 3.11).

The subject will self-administer study drug once daily in the morning to the shoulder(s) and upper arm(s). The study drug should not be administered to other parts of the body, including abdomen, genitals, chest, armpits (axillae), or knees. See Figure 1 for acceptable application sites.

Figure 1. Study Drug Application Sites

Following study drug administration, the subjects should wash their hands with soap and water. After the study drug has completely dried, the subject should cover up the application site with a t-shirt.

6.5 Study Drug Adherence

Subjects will be instructed to return all used or unused bottles at each visit to determine adherence via bottle weight. At each of the visits as specified in Section 2.1, the study coordinator will question the subject regarding adherence to the assigned regimens. A weight measurement of the study drug pump bottle will be conducted. Study drug lot number, the date that the study drug bottle(s) were dispensed/returned, and the weight of the returned study drug bottles will be recorded. The bottle weight of the returned study drug bottles will be compared to an average bottle weight to determine adherence. The number of doses that should have occurred between visits will be calculated. Subjects with adherence values below 85% or above 120% adherence will be re-instructed on proper use and informed of the importance of adherence to continue in the study. An overall accountability of study drug will be performed and verified by AbbVie/designee.

7 Appendices

7.1 ABPM Collection Validity Criteria

The ABP monitor will be set to automatically measure and record BP every 30 minutes for 24 hours. A 24-hour ABPM collection will be considered valid if all of the following are obtained:

1. At least 24 measurements of SBP during the 24-hour period
2. At least 12 SBP measurements between 09:00 and 21:00
3. At least 5 SBP measurements between 01:00 and 06:00

7.2 Cuff Size and Office Blood Pressure Measurements Instructions

1. Measure subject's arm by wrapping a tape measure around the subject's bicep at mid-arm to determine the arm circumference (measured inches or cm).
2. Select a proper cuff size based on arm circumference.

The ideal cuff bladder length is ≥ 80 percent of the subject's arm circumference. The ideal cuff bladder width is ≥ 40 percent of the subject's arm circumference.

Key Steps for Proper BP Measurements	**Specific Instructions**
Step 1: Properly prepare the subject	1. Have the subject relax, sitting in a chair (feet flat on the floor and legs uncrossed, back straight and supported) for > 5 min. 2. The subject should avoid caffeine, caffeinated beverages, exercise, and smoking for at least 30 minutes before measurement. 3. Ensure subject has emptied his bladder. 4. Neither the subject nor the observer should talk during the rest period or during the measurement. 5. Remove all clothing covering the location of cuff placement. 6. Do not measure BP while the subject is sitting or lying on an examining table.
Step 2: Use proper technique for BP measurements	1. Use an automated oscillometric device. 2. Support the subject's arm (e.g., resting on a flat surface such as a desk or table, with the upper arm at heart level). 3. Position the middle of the cuff on the subject's upper arm at the level of the right atrium (the midpoint of the sternum). 4. Use the correct cuff size, such that the bladder encircles 80% of the arm, and note if a larger- or smaller-than–normal cuff size is used.
Step 3: Take the proper BP measurements	1. At the first visit, record BP in both arms. Use the arm that gives the higher reading for subsequent readings. 2. Separate repeated measurements by approximately 2 minutes.
Step 4: Properly document accurate BP readings	1. Record SBP and DBP. 2. Document the time of most recent BP medication taken before measurements.
Step 5: Average the readings	Two or 3 readings will be averaged. If the first 2 readings differ by more than 5 mmHg, additional readings will be obtained and averaged. The average BP reading should be recorded.

BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure

Adapted from Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):e13-115.