CLINICAL STUDY PROTOCOL

A 12-Month, Randomized, Active-controlled, Open-label Study of the Efficacy and Safety of Oral Testosterone Undecanoate in Hypogonadal Men

Protocol Number:	MRS-TU-2019
EudraCT Number:	Not Applicable
INC Research, LLC a Syneos Health Company, Health Study Number:	1005416
Investigational Product:	SOV2012-F1
Phase:	Phase 3
Sponsor:	Marius Pharmaceuticals 8601 Six Forks Road Suite 630 Raleigh, NC 27615-2965 United States
Contract Research Organization:	INC Research, LLC a Syneos Health Company 3201 Beechleaf Court Suite 600 Raleigh, NC 27604-1547 United States
Protocol Date:	18 February 2019
Protocol Version:	Version 9.0

PROTOCOL HISTORY

Version	Brief Description of changes	Date
New, Version 1.0	Original submitted to FDA	01 Mar. 2017
Amendment 1 Version 2.0	First version submitted to IRB. The time window for the single time point blood draw was changed from 3 to 5 hours to 'to be determined from the efficacy data'. Other changes added to clarify study procedures. Added use of ASA24 to collect diet information. Added exclusion criterion related to gynecomastia within last 6 months. Added instruction to take SOV2012-F1 medication 30 minutes after start of meal.	10 May 2017
Amendment 2 Version 3.0	Per FDA feedback, the titration scheme changed from using 24-hour PK parameters C_{avg} and C_{max} to using single time point testosterone levels obtained 3 to 5 hours post-morning dose. Titration decisions will be based on an algorithm derived from Phase 2b data. Thresholds for titration set to 235 ng/dL and 1400 ng/dL. This algorithm is applied during the 24-hour PK sampling on Days 14 and 42 and during safety period. Screening testosterone level to 281 ng/dL from 300 ng/dL to align with reference range for T screening assay. Added ACTH stimulation sub-study. Defined Full Analysis Set population as any subject receiving at least one dose of SOV2012-F1. Added language to clarify that efficacy measurement will be based on normal range for plasma T bioanalytical method (LC- MS/MS). Added additional PK endpoints as requested by FDA. Details of titration algorithm derivation added as Appendix 16.3.	15 June 2017
Amendment 3 Version 4.0	Per FDA feedback and interim results from normal testosterone range study using the plasma bioanalytical method, the down-titration threshold was decreased from 1400 to 1120 ng/dL. Exclusion criterion #10 modified to specify small bowel resection as exclusionary. Exclusion criterion #16 modified to allow increased hematocrit for patients previously on testosterone replacement therapy with less than 30 days washout.	08 August 2017
	Clarified in synopsis that HbA1c inclusion criterion is less than 8.0%.	

Version	Brief Description of changes	Date
	Clarified BP measurement protocol at study visits – duplicate measurements at all study visits other than those when 24-hour hour PK sampling is performed. Made Schedule of Assessments (table 7.1) consistent with Section 8 (Timing of Study Procedures). Specified that subjects should remain well hydrated during fasting period prior to study visits that involve laboratory testing. Specified that cosyntropin administration in ACTH substudy occurs over 2 -minute period, reconstituted in 2 to 5 ml of saline. Clarified time of dose administration for SOV2012- F1 is 30 ± 5 minutes after start of meal. Revised Appendix 16.3 on derivation for SOV2012-F1 of single time point window and titration thresholds to reflect interim normal range data for plasma assay.	
Amendment 4 Version 5.0	An artefact of increased hematocrit values has been identified, resulting in inaccurate hematocrit values obtained by the central laboratory. This artefact results from a known phenomenon of red blood cells swelling in blood samples as the time after collection increases. The amendment removes hematocrit as an exclusion criterion, and modifies the hemoglobin criterion to be a range, so that it serves the same purpose as the previous hematocrit exclusion criterion. An appendix is added to provide the rationale for use of hemoglobin in place of hematocrit in the exclusion criteria.	18 August 2017
Amendment 5 Version 6.0	The total number of patients anticipated to be screened will be increased from ~700 to ~1850, for the same goal of 300 randomized patients. Approximately 72% of screen failed patients to date failed at screening visit 1. The study has experienced two issues which have led to a lower than anticipated randomization rate. The requirement to decrease the entry total serum Testosterone concentration to < 281 instead of<300 ng/dL, has impacted approximately 13% of those subjects failing screening.	12 January 2018

Version	Brief Description of changes	Date
	New safety measures have been implemented regarding hemoglobin levels greater than 18 g/dL. These measures call for reducing the dose of SOV2012-F1 subjects with hemoglobin greater than 18 g/dL after a retest, or subject withdrawal if already at the lowest dose (200 mg daily dose). For subjects assigned to the AndroGel arm, reduce the dose by one actuation per day, except for subjects at the lowest dose of 20.25 mg per day (one pump actuation) who will be withdrawn. For any subjects who have had dose reductions due to hemoglobin greater than 18 g/dL, the hemoglobin measurement should be repeated 30 days after the dose reduction (plus/minus seven days). A new safety measure for prostate-specific antigen (PSA) has been implemented. For any on-study increase in PSA $\geq$ 0.8 ng/mL from the Visit 2baseline result, retest the PSA within 2 weeks of the test revealing the increased result. If the repeat measurement confirms an increase in PSA $\geq$ 0.8ng/mL, consult the subject's urologist and primary care provider regarding historical PSA values and history of prostate health, in order to determine if the subject can safely continue in the study. Withdrawn subjects should be scheduled for follow-up by their primary care provider and/or urologist. Text has been added to describe the process used for determining low-density lipoprotein (LDL) values for comparison to inclusion criterion 5c. If the triglyceride result falls outside the valid range for the central lab calculation of LDL, then an additional sample is obtained for direct measurement of LDL. This requires an additional sample to be taken before Visit 3. The allowable windows for Visit 1 (screening), Visit 2 (screening) and Visit 3(randomization) have been adjusted so that Visit 3 always takes place within 10 days of Visit 2. Additionally, the description of timing of Visits 4 through End of Study have been clarified to match actual practice.	

Version	Brief Description of changes	Date
	For pre-dose blood pressure measurements at Visits 4, 6, and 8 for 24-hour PK measurement, a 60- minute window prior to dosing is defined for obtaining the initial BP measurement. This allows the BP to be taken before eating.	
	Minor formatting changes have been made without change to content or meaning.	
Amendment 6 Version 7.0	An extension study (MRS-TU-2019EXT) has been added as Appendix 16.12. Its purpose is to further examine the BP effects of SOV2012-F1, using 24-hour ambulatory blood pressure monitoring (ABPM). A secondary objective will be to demonstrate the feasibility of using a lower starting dose of SOV2012-F1 (daily dose of 400 mg [200 mg with breakfast meal and 200mg with dinner meal]) to minimize the number of subjects exposed to a higher starting dose than is needed. Another secondary objective is to collect a single set of samples to evaluate bioanalytical effects of serum versus plasma samples. Approximately 135 men who complete the 52-week study, MRS-TU- 2019, and are willing to consent to participate in the extension study will be eligible to participate. Study Procedures and Schedule of Assessments for D365 will be revised to include the assessments required for MRS-TU-2019EXT as well as information for D364 will be added for those subjects continuing in the extension study. Adding information for the 100 mg and 150 mg SOV2012-F1 strengths to Section 7.4.2 Identity of Investigational and Comparator Products. Adding analysis of HbA1c at D365 for MRS-TU- 2019 subjects (from an already planned and collected hematology sample at D365). Addition of sample collection for bioanalytical sample stability from 12 or more SOV2012-F1 subjects in MRS-TU-2019, at Visit 10 (Day 180) or Visit 12 (Day 270).	27 June 2018
	Changing INC Research to INC Research, LLC a Syneos Health Company, due to a merger with inVentiv.	

Version	Brief Description of changes	Date
Amendment 7 Version 8.0	For Bioavailability sample Stability Substudy (BSSS), an unscheduled option was given for the sampling visit, within one week of either Visit 10 for Visit 12. This was done to accommodate some subjects who experienced dose level changes making them eligible, on the morning of the associated visit and could not extend the visit without notice. Eligibility Criteria for BSSS sampling study was revised to Hgb >13g/dL, from >14g/dL. Per FDA feedback, the ABPM MRS-TU-2019EXT study has been extended to provide ABPM data collection after 4 months of treatment at a subject's final dose. Subjects are expected to reach their final dose by Day 28E or Day 56E and remain on that dose throughout the remainder of the treatment. The overall treatment period was extended to 6 months total to provide a minimum 4-month treatment period at final dose for all subjects. The visit schedule and objectives have been revised to align with the extended 6-month treatment period. Per FDA feedback the enrollment target for the MRS- TU-2019EXT was increased from 135 enrolled to up to approximately 170 enrolled, with a target completion of 135 evaluable subjects at 4 months of treatment. Site participation numbers were also increased in an effort to enroll larger subject numbers. A pathway for enrollment into MRS-TU-2019EXT ABPM extension study was added for subjects having already completed MRS-TU-2019 by the start of MRS-TU-2019EXT, whereby subjects could enroll, bypassing the D364-365 requirements and beginning participation at the required 8-week washout visits. An option has also been added to enroll non-MRS-TU-2019 subjects, from a few select sites, to the ABPM extension study in order to increase the likelihood of reaching the desired total number of participating subjects in MRS-TU-2019EXT. There are revisions to which MRS-TU-2019EXT ABPM extension study visits require fasting to assure in-clinic BP is measure in a fasted state across all visits which include vital signs. An addition of a "no	09 Oct 2018

Version	Brief Description of changes	Date
	smoking within 30min of the start of the study visit" was added to avoid impact of smoking on in-clinic BP assessments. The prior requirement of a "passing" ABPM assessment at Day365/Visit 2E (EOT main MRS-TU- 2019study) was removed. The requirement for "passing" ABPM assessment was added to Visit 7E/ Day1E of treatment in the extension study, because this timepoint is considered necessary as the baseline from which to measure changes during the ABPM extension study. Per FDA request for MRS-TU-2019EXT, ABPM Extension Study only: added Eligibility Inclusion limitation for MRS-TU-2019EXT, for newly enrolled subjects of BP≤ 140/90, and requirement for all subjects to have BP ≤140/90 in order to continue past Visit 6E to dosing. Clarified Exclusion Criteria for ABPM Extension Study Only, Newly Enrolled Subjects: main study exclusion criteria #2: patients *must not have received prior testosterone replacement therapy within 8 weeks* of the start of the study, with the exception of T implantable pellets which are excluded for 6 months. ***For ABPM Extension Study Only: Newly Enrolled Subjects to MRS-TU-2019EXT ABPM Extension Study**, patients *must not have received prior testosterone replacement therapy within 8 weeks* of the start of the study, with the exception of T implantable pellets which are excluded for 6 months.	

Version	Brief Description of changes	Date
Amendment 8 Version 9.0	Removed CBG analysis from the ACTH sub-study time-zero sample on Day 365. Replaced the FTZ method of Free T calculation with the FTV method. Clarified that added Eligibility Inclusion limitation for MRS-TU-2019EXT, for newly enrolled subjects of BP< 140/90, and requirement for all subjects to have BP < 140/90 at V6E in order to continue to V7E dosing, is based on in-clinic BP assessment (average of those assessments required for the visit). Clarified that if new enrollment subjects have a normal physical exam at Screening V2(EXT), they are not required to have a repeat physical exam at V7E. Added the clarifications stated in the 23 October 2019, Protocol V8.0 Clarification Letter: At selected new enrollment centers, subjects who completed the main MRS-TU-2019 study > 8 weeks prior and had not yet entered into MRS-TU-2019EXT, may be enrolled as a new enrollment subject, providing they meet all eligibility criteria specified for new enrollment subjects. This removes the requirement of an additional 8-week washout period for prior subjects off of treatment for 8 or more weeks already. Clarified additional information being collected in the CRF at time of 24-hr ABPM readings, i.e., the eCRF will collect basic information about any unusual events that may impact BP, as follows: Did the subject experience any of the following during this 24-hour home BP monitoring period? • Unusual activity? • Unusual diet? • Unusual stressful event?	18 Feb 2019

Version	Brief Description of changes	Date
	Unusual events are described as those events that are unusual to the individual subject's activities or experiences of daily living. Added a 24-hr Serum T /DHT substudy for select centers in ABPM Extension Study MRS-TU-2019EXT (approximately 100 subjects), to include added Serum T collection at all 24-hr PK timepoints at V12E/D90E for up to approximately 100 subjects. Added definitions of analysis populations for MRS-TU-2019EXT. Added efficacy (Cavg and Cmax) analyses to primary and secondary objectives of MRS-TU-2019EXT. Removed LiHeparin tubes from sample collection for bioanalytical analysis. Added exploratory analysis of serum T and DHT values obtained at V12E/D90E in the serum sub-study. Added exploratory analysis of titration decisions comparing all sample types.	

1. PROTOCOL APPROVAL SIGNATURES

Protocol Title: A 12-Month, Randomized, Active-controlled, Open-label Study of the Efficacy and Safety of Oral Testosterone Undecanoate in Hypogonadal Men

Protocol Number: MRS-TU-2019

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation of Technical Requirements for Human Use (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatory

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Chief Executive Officer 8601 Six Forks Road Suite 630
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Date

2. SYNOPSIS AND TABLE OF CHANGES

Protocol Number:

MRS-TU-2019

Title: A 12-Month, Randomized, Active-controlled, Open-label Study of the Efficacy and Safety of Oral Testosterone Undecanoate in Hypogonadal Men

Investigational Product:

SOV2012-F1, a novel, oral preparation of testosterone undecanoate (TU)

Study Centers: 35/United States

Phase: Phase 3

Objectives:

Primary Objective:

- To determine the efficacy of oral SOV2012-F1 as measured by the percentage of male hypogonadal subjects with average plasma total testosterone (T C_{avg}) within the normal range after 90 days of treatment.

Secondary Objective:

- To determine the percentage of SOV2012-F1–treated subjects with maximum plasma testosterone concentration (T C_{max}) values (a) < 1500 ng/dL; (b) 1800 to 2500 ng/dL; and (c) > 2500 ng/dL after 90 days of treatment.

Exploratory Objectives:

- To determine change from baseline in the following subject-reported outcomes by SOV2012-F1–treated and AndroGel® (testosterone gel) 1.62%–treated subjects after 52 weeks of treatment: International Prostate Symptom Score (I-PSS), Psychosexual Daily Questionnaire (PDQ), Short-Form Survey (SF-36), and International Index of Erectile Function (IIEF).
- To determine change from baseline in fasting serum glucose and fasting insulin concentrations in SOV2012-F1–treated and AndroGel 1.62%–treated subjects after 52 weeks of treatment.
- To determine the stability of blood samples to support identification of sample types and handling necessary for accurate testosterone measurements with oral TU administration.

Safety Objectives:

- To determine the incidence of adverse events (AEs), serious adverse events (SAEs), and AEs leading to study withdrawal in SOV2012-F1–treated subjects compared with AndroGel 1.62%–treated subjects after 52 weeks of treatment.

- To assess change from baseline in blood pressure (BP), liver function tests, hematology parameters, hormone levels, lipid profiles, and serum prostate-specific antigen (PSA) in SOV2012-F1–treated and AndroGel 1.62%–treated subjects after 52 weeks of treatment.
- To determine the effect of SOV2012-F1 on adrenal cortical function as assessed by measuring the cortisol response to synthetic ACTH at baseline and after 52 weeks of treatment in a subset of 30 SOV2012-F1 subjects and 15 AndroGel subjects.

Study Design:

MRS-TU-2019 will be a randomized, multi-center, open-label, active-controlled, efficacy (based on T C_{avg} and T C_{max}), and safety study in adult hypogonadal men. The study duration is 12 months (365 days), including a 90-day, open-label efficacy period and a 9-month (275- day) safety evaluation period. All study days should be understood to be ±2 days for Visits 4, 5, 6 and 7 (e.g., Visit 4, Day 14 may occur from Day 12 of the study period to Day 16) in the titration period and ±3 days beginning with Visit 8, (Day 90) to the Follow-up Visit. These day ranges for each visit are designated in the Schedule of Assessments (Table 7-1), Overall Study Design figures (Figure 7-1 and Figure 7-2), and Timing of Study Procedures (Section 8), but are generally not designated throughout the text of this protocol.

Study MRS-TU-2019EXT is an extension to study MRS-TU-2019, detailed in Appendix 16.12. Its purpose is to further examine the BP effects of SOV2012-F1 using 24-hour ambulatory blood pressure monitoring (ABPM). The duration of the Extension Study (MRS-TU- 2019EXT) is approximately 8.5 months (255 days). This includes an 8-week washout period, an assessment of ambulatory BP before treatment start, at 4-months and 6-month (180 days) treatment period and a one-week safety follow-up. The 6-month ABPM visit will provide data on stabilization of ambulatory BP, following the 4-month data for the ambulatory BP primary endpoint. *For details of the extension study design and procedural requirements, please refer to Appendix 16.12.*

MRS-TU-2019 Study:

Enrollment into the MRS-TU-2019 study will be based on selection criteria designed to reflect the general population of hypogonadal men. Subjects must be naïve to androgen replacement therapy or washed out adequately of prior androgen replacement therapies.

Subjects will undergo 2 screening visits (Screening Visit 1 and Screening Visit 2) during the study screening period to verify inclusion and exclusion criteria. Subjects must have 2 consecutive serum total testosterone (T) levels ≤ 281 ng/dL based on a blood sample obtained from 7 a.m. to 10 a.m., drawn on separate days, at least 3 days apart. Furthermore, subjects must have at least 1 clinical feature consistent with male hypogonadism. Those subjects taking commercial testosterone replacement therapy (TRT) currently must have a history of at least 1 clinical feature consistent with male hypogonadism.

Hematocrit, when analyzed by a central laboratory with consequent delay between sample collection and evaluation, has been shown to be unreliable and to result in higher than true values. A range of hemoglobin (Hgb) values is used to exclude subjects with abnormal

hemoglobin or with abnormal hematocrit by using hemoglobin as a surrogate for hematocrit.

Eligible subjects will be randomized 2:1 (approximately 200 SOV2012-F1–treated subjects to 100 AndroGel-treated subjects, respectively) and stratified by study center to receive SOV2012- F1 or AndroGel 1.62%, a commonly prescribed topical T replacement product, hereafter referred to as AndroGel. Both treatments will be continued for the 12-month study duration, and the comparator, AndroGel, will be used only for assessment of safety.

Testosterone measurements in subjects receiving SOV2012-F1, which contains TU (a T prodrug), will be made using plasma samples. The sampling tubes contain an enzyme inhibitor to prevent post-blood collection conversion of TU to T. Measurements of T for AndroGel will be made using serum samples, as per product information.

SOV2012-F1 will be started at a total daily dose of 600 mg (400 mg with the morning meal and 200 mg with the evening meal). The plasma T concentration between 3 to 5 hours at Visit 4, Day 14 and Visit 6, Day 42 will determine the need, if any, to adjust the dose up or down by 200 mg at Visit 5, Day 28, and Visit 7, Day 56, respectively. The minimum dose of SOV2012-F1 will be 200 mg with the morning meal and no evening dose. The maximum dose of SOV2012-F1 will be 1000 mg, as 600 mg with the morning meal and 400 mg with the evening meal.

The study of bioanalytical sample stability will be made using samples from at least 12 subjects in the SOV-2012-F1 arm of MRS-TU-2019. Samples will be collected depending on date of subject consent at either Visit 10 (Day 180) or Visit 12 (Day 270), or at an unscheduled visit within one week of either visit. Subjects will be fed a high-fat, in-clinic breakfast of at least 700kcal 30-min prior to dosing. The purpose of this substudy is to assess the stability of samples containing TU, which may be hydrolyzed to T ex-vivo.

AndroGel will be applied at a starting dose of 40.5 mg once daily (QD). The serum T predose concentration (T $C_{predose}$) from a single blood draw at Day 14 and Day 42 will determine the need, if any, to titrate per the product information [1, Section 16.4] at Day 28 and Day 56, respectively.

The final doses established in the efficacy period for SOV2012-F1 and AndroGel will be used at the start of the 9-month safety evaluation period. The dose of SOV2012-F1 may be up- or down-titrated on Day 180 and Day 270 based on the plasma T concentration from a single blood draw within 3 to 5 hours after the morning dose (Day 166 and Day 256). Subjects on AndroGel may be up- or down-titrated on Day 180 and Day 270 based on single-draw serum T $C_{predose}$ levels at Day 166 and Day 256, per product information.

If analysis of the Day 90 24-hour PK data reveals that a subject is on an incorrect dose, discontinuation of the subject may be appropriate in the following instances:

- A SOV2012-F1–treated subject has been previously down-titrated to 200 mg in the morning only, and T C_{max} is > 2500 ng/dL on Day 90: the subject will be discontinued, as continuation in the study will expose the subject to repeated T C_{max} values > 2500 ng/dL.

- A SOV2012-F1–treated subject has been up-titrated to 1000 mg, and T C_{avg} is below the normal range (2.5% percentile) on Day 90: the subject may be discontinued if, in the opinion of the investigator, continuation in the study would expose the subject to an investigational treatment without probability of successful treatment.

If a SOV2012-F1–treated subject has T C_{avg} below the normal range (2.5% percentile) on Day 90 the subject may be dose-titrated at an unscheduled visit, if the efficacy period data suggests benefit to the subject and an acceptable safety profile.

Titration decisions will be communicated through Interactive Web Response Technology (IWRT).

A Schedule of Assessments is provided in Table 7-1. More information about dose titration is provided in Section 7.4.7, Figure 7-1, and Figure 7-2.

Diet

For 24-hour PK collection visits, subjects will be dosed and fed in the clinic and will remain until after the final PK or safety assessment. SOV2012-F1–treated subjects will be confined to the clinic on Day 14 to Day 15, Day 42 to Day 43, and Day 90 to Day 91, for Visit 4, Visit 6, and Visit 8, respectively. AndroGel-treated subjects will be confined to the clinic only from Day 90 to Day 91 for Visit 8. Subjects will be provided with breakfast at all visits that require fasted blood draws, and breakfast, lunch, and dinner during 24-hour PK collection visits.

Meals provided will be consistent with their standard eating habits as documented by the Automated Self-Administered 24-Hour Recall (ASA24) system, developed by the National Institutes of Health [2,3]. For the SOV2012-F1 study arm, subjects should ingest the medication 30 (±5) minutes after the start of the meal.

At Screening Visit 1, all subjects will receive a meal diary to record three days of breakfasts and dinners prior to visit 2. The study coordinator at each site will enter the diary-recorded meals in to the ASA24 system in the presence of the subject for assessing total calorie and fat intake for each meal type. Based on the results, SOV2012-F1 subjects will be assigned to 1 of the following 3 meal categories at visit 3 for breakfast and dinner as the drug must be taken with the morning meal and the evening meal:

- low-fat meals (≤20% calories from fat),
- normal-fat meals (>20% to 35% calories from fat),
- high-fat meals (>35% calories from fat).

Subjects in the SOV2012-F1 study arm will receive breakfast, and dinner on Days 14, 42, and 90 in the clinic according to the meal categories based on the ASA24 system report (all lunches will be normal fat). If the average reported fat content for a given meal (breakfast or dinner) is ≤ 20%, subjects will receive low-fat meals; if > 20% to ≤ 35%, subjects will receive normal-fat meals; and if > 35%, subjects will receive high-fat meals. Assignments are per meal type (e.g., a subject may receive a breakfast with different fat content than dinner, depending on his recorded eating patterns). All lunches will be normal fat (30% to 35% calories from fat) as no dosing occurs with the lunch meal. SOV2012-F1 lunch compliance will not be recorded in the eCRF. Subjects will be provided light snacks upon their request in the afternoon and after dinner as long as it is 2 hours before or after dosing

meals, in order to minimize the effect on subjects completing their meals fully at relevant dosing meals.

Subjects will receive breakfast at fasted Visit 3, however, because there is no PK measurement after the first dose, subjects may choose from any normal fat breakfast offered by the site.

SOV2012-F1- treated subjects coming to the clinic after V3 for fasted and PK assessments (single visit days or confinement days) will receive breakfast and dinner meal choices as assigned by ASA24 records. The subject's meal choice, meal fat type, and the percentage of meal consumed (0, 25%, 50%, 75%, 100%), will be recorded in the subject's electronic case report form (eCRF).

AndroGel-treated subjects, who subsequently visit the clinic after V3, for fasted days or for their confined clinic day for 24-hour PK sampling (Day 90 to Day 91, will receive meals of choice, selected form the normal fat menus according to the ASA24 system report.

All Subjects may be offered normal fat breakfast at the end of 24-hour PK days providing it is after all relevant fasting/PK draws and that day's dosing is 30 (±5) min after meal start.

Additional meal and food intake procedures are described in the Schedule of Assessments (Table 7-1) and Section 8 (Timing of Study Procedures).

Number of Subjects:

Approximately 1850 subjects are planned to be screened, and 300 subjects are planned to be randomized to receive open-label treatment in a 2:1 ratio, stratified by study center.

Approximately 200 subjects will be randomly assigned to receive SOV2012-F1, and approximately 100 subjects will be randomly assigned to receive AndroGel). At least 12 SOV2012-F1 subjects from MRS-TU-2019, will be enrolled in the Bioanalytical Sample Stability Substudy.

Treatments:

- SOV2012-F1 will be started at a total daily dose of 600 mg (400 mg with the morning meal and 200 mg with the evening meal) and titrated, if needed, according to the dose-titration algorithm established in this protocol.
- AndroGel will be applied at a starting dose of 40.5 mg in the morning and titrated, if needed, according to dose-titration algorithm in the approved product information.

Study Duration:

The study duration is 12 months (365 days), including a 90-day, open-label efficacy period and a 9-month (275-day) safety evaluation period.

Study Population:

Key Inclusion Criteria:

1. Male aged 18 to 65 years, inclusive, at the time of providing informed consent to participate in the study.
2. Hypogonadism defined as having 2 consecutive serum total T levels ≤ 281 ng/dL based on a blood sample, drawn at least 3 days apart, between 7 a.m. and 10 a.m.
3. At least 1 clinical feature consistent with male hypogonadism. If a subject is receiving commercial TRT prior to Screening Visit 1, he must have a history of at least 1 clinical feature consistent with male hypogonadism.
4. Must be naïve to androgen replacement therapy or washed out adequately of prior androgen replacement therapies; willing to cease current T treatment; or currently not taking any T treatment. Subjects must remain off all forms of T, except for dispensed study drug, throughout the entire study.
5. No unstable ongoing concomitant medical conditions. Treated and well-controlled conditions such as type 2 diabetes, hypertension, or dyslipidemia are acceptable with stable medication in place for at least 3 months prior to study entry:
    a. Hemoglobin A1c < 8.0%
    b. BP < 150/90 mm Hg
        - *for MRS-TU-2019EXT ABPM Extension Study, the in-clinic, average BP must be ≤ 140/90 for inclusion into the MRS-TU-2019EXT study.
    c. Low-density lipoprotein cholesterol < 190 mg/dL.
6. Subjects with an endocrine disorder requiring treatment other than hypogonadism must be on a stable dose of replacement medication for at least 3 months prior to study entry.
7. Adequate venous access to allow collection of a number of blood samples via a venous cannula.
8. Written informed consent to participate in the study and ability to comply with all study requirements.
9. **For Bioanalytical Sample Stability Substudy only**: Must be on SOV2012-F1 dose of at least 400mg in AM (600 or 800mg total daily dose) at date of consent.

Key Exclusion Criteria:

1. Serum PSA > 2.5 ng/ml and/or abnormal prostate gland on palpation, e.g., palpable nodes, at Screening Visit 2.
2. Received oral, topical, intranasal, or buccal T therapy within the previous 2 weeks, intramuscular T injection of short-acting duration within the previous 4 weeks, intramuscular T injection of long-acting duration within the previous 20 weeks, or T implantable pellets within the previous 6 months.

   ***For ABPM Extension Study Only: Newly Enrolled Subjects to MRS-TU-2019EXT ABPM Extension Study**, patients *must not have received prior testosterone replacement therapy within 8 weeks* of the start of the study, with the exception of T implantable pellets which are excluded for 6 months.

3. Use of any drug that could interfere with measurement or assessment of serum androgen levels, including 5 alpha-reductase inhibitors, anabolic steroids, and drugs with antiandrogenic properties (e.g., spironolactone, cimetidine, flutamide, bicalutamide, and ketoconazole). These drugs must be stopped for at least 1 month prior to study entry (6 months in the case of dutasteride). Patients taking potent, long- acting opiate therapy on a daily basis are not eligible for the study. Conversely, ad hoc use of potent, short-acting opiates for a period of less than 7 days may be permitted after discussion with the Marius Pharmaceuticals medical monitor.
4. Use of over-the-counter products, including natural health products (e.g., food supplements and herbal supplements such as saw palmetto or phytoestrogens) that may affect total T levels, within 7 days prior to study entry.
5. History of drug or alcohol abuse within the past 2 years that in the opinion of the investigator could interfere with study participation and/or influence study efficacy and safety endpoints assessments.
6. Unstable or chronic disease that could interfere with participation in the study or patient safety, including psychiatric disorders.
7. Myocardial infarction, coronary artery surgery, heart failure, stroke, unstable angina, or other unstable cardiovascular disease within the past 6 months.
8. Abnormal ECG considered clinically significant by investigator at Screening.
9. Diagnosis of any cancer within the previous 5 years other than basal or squamous cell skin cancer with clear margins.
10. Any surgical or medical condition that might alter administration of the study drug or comparator, including history of gastric surgery, cholecystectomy, vagotomy, small bowel resection, or any surgical procedure or medications (e.g., GLP-1 agonists and motility agents such as domperidone, metoclopramide, etc.) that might interfere with gastrointestinal motility, pH, or absorption of TU.
11. Duodenal or gastric ulcers, or gastrointestinal/rectal bleeding during the 3 months prior to screening.
12. Chronic skin conditions on the chest or upper arms that would prevent administration of AndroGel in a manner designed to ensure reliable and consistent absorption thereof.
13. Human immunodeficiency virus (HIV) infection.
14. Chronic hepatitis B virus and/or hepatitis C virus (HCV) infection (as determined by positive testing for hepatitis B virus surface antigen or HCV antibody with confirmatory testing, i.e., detectable serum HCV ribonucleic acid [RNA]).
15. Clinically significant abnormal laboratory values at screening including but not limited to:
    a. Elevated liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT] > 2X upper limit of normal)

b. Estimated glomerular filtration rate < 60 ml/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease formula

c. Hemoglobin < 11.0 g/dL or > 16.0 g/dL. For a subject previously on testosterone replacement therapy with less than 30 days washout prior to screening Visit 2, hemoglobin < 11.0 g/dL or > 17.0 g/dL.

16. ~~Hematocrit > 48%. For subjects previously on testosterone replacement therapy with less than 30 days washout prior to screening Visit 2, hematocrit > 50%.~~
NOTE: Exclusion criteria #16 removed with Version 5.0 of Protocol. Numbering retained for clarity of records.

17. Severe or untreated obstructive sleep apnea syndrome.

18. Severe lower urinary tract symptoms (American Urological Association/ IPSS ≥ 19).

19. History of any clinically significant illness, infection, or surgical procedure within 1 month prior to study entry.

20. Past, current, or suspected prostate or breast cancer.

21. History of long QT syndrome or unexplained sudden death in a first-degree relative (parent, sibling, or child).

22. Concurrent treatment with medications that may impact the absorption, distribution, metabolism, or excretion of TU or place the subject at risk for treatment with T.

23. Subject has a partner who is currently pregnant or planning pregnancy during the course of the study.

24. Treatment with any other investigational drug within 30 days of study entry or > 5 half- lives (whichever is longer) and at any time during the study.

25. History of noncompliance to medical regimens or potential unreliability in the opinion of the investigator.

26. Unwilling or unable to comply to the dietary requirements for this study.

27. History of polycythemia, either idiopathic or associated with TRT.

28. Donated blood (≥ 500 mL) within the 12-week period prior to study entry.

29. History of an abnormal bleeding tendency or thrombophlebitis within the previous 2 years that is not linked to venipuncture or intravenous cannulation.

30. Onset of gynecomastia within the previous 6 months.

31. **For ACTH Stimulation Substudy only**: Primary or secondary adrenal insufficiency.

32. **For Bioanalytical Sample Stability Substudy only**: subjects with a hemoglobin <u>less than 13 g/dL at most recent assessment* [should be excluded]</u>.

Primary Endpoint:

Percentage of SOV2012-F1–treated subjects with a plasma T C_{avg} within the normal range after 90 days of treatment

Secondary Endpoints:

Percentage of SOV2012-F1–treated subjects with plasma T C_{max} values that are (a) < 1500 ng/dL; (b) 1800 to 2500 ng/dL, and (c) > 2500 ng/dL after 90 days of treatment

Exploratory Endpoints:

- Change from baseline in the following patient-reported outcomes by SOV2012-F1– treated and AndroGel-treated subjects, after 52 weeks of treatment: I-PSS, PDQ, SF- 36, and IIEF.
- Change from baseline in fasting glucose and fasting insulin concentrations in SOV2012-F1–treated and AndroGel-treated subjects after 52 weeks of treatment
- Stability of serum and plasma samples subjected to different processing times, processing temperatures, and sample collection tubes types

Safety Endpoints:

- Incidence of AEs, SAEs, and AEs leading to study withdrawal in SOV2012-F1– treated compared with AndroGel-treated subjects after 52 weeks of treatment
- Serum cortisol response to intravenous administration of synthetic ACTH
- Change from baseline in BP and the following laboratory parameters in SOV2012- F1– treated compared with AndroGel-treated subjects after 52 weeks of treatment:
  - Liver function tests (ALT, AST, total bilirubin, alkaline phosphatase)
  - Hematology parameters (hemoglobin)
  - Hormone levels (luteinizing hormone [LH], follicle-stimulating hormone [FSH], dihydrotestosterone [DHT], sex hormone–binding globulin [SHBG], and TSH)
  - Lipid profiles (high-density lipoproteins, low-density lipoproteins, total cholesterol, and triglycerides)
  - Serum PSA

Efficacy:

Efficacy assessments include T C_{avg} and T C_{max}.

Pharmacokinetics:

PK assessments include the calculation of these parameters: maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration-time curve from time (AUC_{0-24}, AUC_{0-12}, AUC_{12-24}, and C_{avg}) for plasma total T, DHT, TU, dihydrotestosterone undecanoate (DHTU), and E2. The DHT/T ratio will be calculated for C_{avg}, AUC_{0-12}, and AUC_{12-24}. Additional parameters may be calculated as deemed necessary. Calculated free testosterone (free T) will be reported for Day 90.

Safety:

Safety assessments include:

- Adverse event monitoring
- Physical examinations including I-PSS
- Vital signs
- Laboratory results
- Serum cortisol response to intravenous administration of synthetic ACTH

Safety retesting parameters include:

- For any on-study Hemoglobin level that is >18 g/dL, the hemoglobin should be re-tested within two weeks of the original test. If the second value is > 18 g/dL, the dose is reduced or the subject withdrawn (if at lowest dose for either study medication).
- For any on-study increase in PSA ≥ 0.8 ng/mL from the baseline Visit 2 result, the PSA should be retested within two weeks of the test revealing the increased result. If an increase of ≥ 0.8 ng/mL is confirmed, the subject's primary physician and/or urologist will be consulted to determine whether the subject can safely continue in the study or should be withdrawn.

Statistical Analysis:

Statistical analyses will be performed on the following populations:

- Full Analysis Set (FAS): This population consists of all subjects randomized into the study and receiving at least one dose of correctly assigned study medication.
- PK Population: The PK population consists of all subjects in the study who have at least 1 evaluable PK profile (calculable C_{max} and C_{avg}) and no significant protocol deviations.
- Efficacy Completers Population: This population consists of all subjects in the PK population who have evaluable C_{avg} and C_{max} from the 24-hour PK assessment obtained at Visit 8, Day 90, and no significant protocol deviations.
- Safety population: The safety population consists of all subjects who took at least
- 1 dose of study drug (SOV2012-F1 or AndroGel).

- ACTH Analysis Set: consists of all subjects randomized into the ACTH substudy.

Statistical outputs will include descriptive tabular and/or graphical summarizations by randomized treatment group and dose received at the time of assessment, if applicable. In general, continuous variables will be presented using descriptive statistics (number of observations [n], mean, standard deviation, standard error of mean, median, and minimum and maximum values) and categorical values will be summarized with counts and percentages.

All collected data will be presented in listings.

The primary efficacy endpoint is the percentage of SOV2012-F1–treated subjects with a plasma T C_{avg} within the normal range after 90 days of treatment.

The 24-hour T C_{avg} will be calculated as the 24-hour area under the concentration-time curve (AUC) divided by the actual number of hours between dosing and the 24-hour sample collection time. The AUC_{0-24} will be calculated using noncompartmental methods. The percentage of subjects randomly assigned to SOV2012-F1 whose 24-hour C_{avg} is within the defined normal range for total T will be calculated. Missing C_{avg} values will be imputed using multiple imputation procedures.

A 95%, 2-sided, binomial confidence interval (CI) surrounding the point estimate will be calculated. The study will have shown effectiveness of SOV2012-F1 if ≥ 75% of the Full Analysis Set population has plasma T C_{avg} in the normal range after 90 days of treatment, with the lower bound of the 95% CI ≥ 65%.

As a secondary endpoint, PK safety will be evaluated by estimating the percentage of SOV2012-F1–treated subjects at Visit 8, Day 90 with: (a) T C_{max} ≤ 1500 ng/dL; (b) T C_{max} >1800 to ≤ 2500 ng/dL; and c) T C_{max} > 2500 ng/dL. The FDA targets for the PK safety parameters are for (a) to be ≥ 85% of subjects, for (b) to be < 5% of subjects, and for (c) to be no subjects. Analyses will be performed using the Full Analysis Set population. Similar analyses will be completed for the AndroGel treatment group.

Pharmacokinetics

The plasma concentrations (TU, DHTU, total T, free T, DHT, and E2) and the derived PK parameters (C_{max}, T_{max}, C_{avg}, and AUC_{0-24}, AUC_{0-12}, AUC_{12-24}, etc.) will be listed by subject by visit day and using the PK Population, summarized with descriptive statistics. The C_{avg}, AUC_{0-12}, and AUC_{0-24} ratios of DHT/T and E2/T will be calculated and summarized with descriptive statistics.

Safety

Using the Safety Population, TEAEs will be summarized and tabulated by system organ class (SOC) and preferred term.

Physical examination results will be summarized at each scheduled visit by treatment and dose received at the visit.

Observed values in vital sign measurements, including systolic blood pressure (sBP), diastolic blood pressure (dBP), heart rate, and weight, and changes from baseline in sBP, dBP, and heart rate, will be summarized at each scheduled visit by treatment and dose within treatment received at each scheduled collection visit.

Observed values and changes from baseline in laboratory test results will be summarized by treatment and dose within treatment at each scheduled visit. Shift tables will be used to evaluate changes in laboratory test values with respect to normal reference ranges. Laboratory tests will be performed at screening and periodically throughout the study.

Table of Changes from Version 8.0 (Seventh Amendment) to Version 9.0 (Eighth Amendment)

Location	Changes
Section 7.5	Remove CBG (cortisol binding globulin) analysis from the ACTH sub-study time-zero sample.
Section 10.4.2.2.1.1	Replaced FTZ method with FTV method for calculation of Free T/
Appendix 16.12 MRS-TU-2019EXT ABPM Extension Substudy **Sections C-G**	For ABPM Extension Study: Clarified that added Eligibility Inclusion limitation for MRS-TU-2019EXT, for newly enrolled subjects of BP≤ 140/90, and requirement for all subjects to have BP ≤140/90 at V6E in order to continue to V7E dosing, is based on **in-clinic** BP assessment (**average** of those assessments required for the visit). Clarified that if new enrollment subjects have a normal physical exam at Screening V2(EXT), they are not required to have a repeat physical exam at V6E. Added the clarifications stated in the Protocol Clarification Letter, 23 October 2018, Protocol V8.0: • At selected new enrollment centers, subjects who completed the main MRS-TU-2019 study ≥ 8 weeks prior and had not yet entered into MRS-TU-2019EXT, may be enrolled as a new enrollment subject, provided they meet all eligibility criteria specified for new enrollment subjects. This removes the requirement of an additional 8-week washout period for prior subjects off of treatment for 8 or more weeks already. • To clarify additional information being collected in the CRF at time of 24-hr ABPM readings, i.e., the eCRF will collect basic information about any unusual events that may impact BP, as follows: *Did the subject experience any of the following during this 24-hour home BP monitoring period?* • *Unusual activity?* • *Unusual diet?* • *Unusual stressful event?* *Unusual events are described as those events that are unusual to the individual subject's activities or experiences of daily living.*
Appendix 16.12 MRS-TU-2019EXT: Section E Timing of Study Procedures, **Treatment Period-All Subjects, V7E**	For newly enrolled subjects who have a normal full physical exam at V2(EXT) screening, it is not required to repeat the full physical exam at V7E, unless there is clinical reason to do so.

Appendix 16.12 MRS-TU-2019EXT: Section A, Overview, and Section E, Timing of Study Procedures (V12E)	Added a 24-hr Serum T/DHT Substudy for select centers (up to approximately 100 subjects), to include added Serum T/DHT sample collection at all 24-hr PK timepoints at V12E/D90E.
Appendix 16.12 MRS-TU-2019EXT: Section E	Clarified that HbA1C will not be analyzed in Early Withdrawal hematology samples
Appendix 16.12 MRS-TU-2019EXT: Section H Statistical Analysis.	Added definitions of analysis populations for MRS-TU-2019EXT. Added efficacy (C_{avg} and C_{max}) analyses to primary and secondary objectives of MRS-TU-2019EXT. Removed LiHeparin tubes from sample collection for bioanalytical analysis. Added exploratory analysis of serum T and DHT values obtained at V12E/D90E in the serum sub-study. Added exploratory analysis of titration decisions comparing all sample types.
Appendix 16.12 MRS-TU-2019EXT: Sections B Objectives, G Study Design and H Statistical Analysis.	Removed the scaling factor γ from the secondary endpoints.

3. TABLE OF CONTENTS

3.1. List of Tables

3.2. List of Figures

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

LIST OF ABBREVIATIONS

ABPM AE	ambulatory blood pressure monitoring adverse event
ACTH	adrenocorticotropic hormone American Heart Association
AHA	
ALT	alanine aminotransferase
ASA24	Automated Self-Administered 24-Hour Recall
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-12}	area under the concentration-time curve from time 0 to 12 hours
AUC_{12-24}	area under the concentration-time curve from time 12 to 24 hours
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
BID	twice daily
BP	blood pressure
C_{avg}	average concentration
$C_{avg[0-12]}$	average concentration from time 0 to 12 hours
$C_{avg[12-24]}$	average concentration from time 12 to 24 hours
CBG	cortisol binding globulin
CI	confidence interval
C_{max}	maximum concentration
dBP	diastolic blood pressure
DHT	dihydrotestosterone
DHTU	dihydrotestosterone undecanoate
E2	estradiol
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	End of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
Free T	calculated free testosterone
FSH	follicle stimulating hormone
GCP	Good Clinical Practice glycosylated hemoglobin
HbA1c	
HCV	hepatitis C virus
HIV HR	human immunodeficiency virus heart rate
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Human Use (ICH)
IIEF	International Index of Erectile Function Questionnaire
IPSS	International Prostate Symptom Score
IRB	institutional review board
IWRS	Interactive Web Response System
ITT	intent-to-treat
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory
opt.	Activities optional

PDQ	Psychosexual Daily Questionnaire
PK	pharmacokinetic
PSA	prostate-specific antigen
QD	once daily required
req.	
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
sBP SD	systolic blood pressure symptom directed
SF-36	Short-Form Survey
SHBG	sex hormone–binding globulin
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
T	testosterone
T C_{avg}	average plasma total testosterone
T C_{max}	maximum plasma testosterone concentration
T $C_{predose}$	serum testosterone predose concentration
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TRT	testosterone replacement therapy
TSH	thyroid-stimulating hormone
TU	testosterone undecanoate

5. INTRODUCTION

5.1. Background

Male hypogonadism is a condition in which testes fail to produce physiological levels of testosterone (T). Primary hypogonadism may result from chromosome abnormality (e.g., Klinefelter syndrome), local testicular surgery/disease, infection, mumps orchitis, radiation, and renal failure. Central, or secondary, hypogonadism involves disruption of the hypothalamic pituitary-testicular axis and may result from hypopituitarism, selective gonadatrophic deficiency, severe systemic illness, or the patient being severely underweight [4].

Hypogonadism is characterized by serum T levels < 300 ng/dL in combination with at least 1 clinical sign or symptom consistent with diagnosis. Signs of hypogonadism include absence or regression of secondary sex characteristics, anemia, muscle wasting, reduced bone mass
or bone mineral density, oligospermia, and abdominal adiposity.
Symptoms of postpubescent hypogonadism include sexual dysfunction (erectile dysfunction, reduced libido, diminished penile sensation, difficulty attaining orgasm, and reduced ejaculate), reduced energy and stamina, depressed mood, increased irritability, difficulty concentrating, changes in cholesterol levels, anemia, osteoporosis, and hot flashes [5].
Testosterone deficiency in men is implicated as a risk factor for metabolic syndrome and type 2 diabetes, and independently associated with individual components of the metabolic syndrome—visceral obesity, insulin resistance, hyperglycemia, hypertension, and dyslipidemia [6]. Epidemiological studies report increased mortality in men with low T [7].

The prevalence of primary hypogonadism in men is best estimated by the prevalence of Klinefelter syndrome, the leading congenital cause of hypogonadism. Prevalence of Klinefelter syndrome is reported to be between 0.1% and 0.2% [8,9]. Reported prevalence rates are most likely to be an underestimate, as it has been recently suggested that 70% to 90% of men with Klinefelter syndrome are never diagnosed during their lifetimes [10]. Furthermore, many cases of hypogonadism appear to be asymptomatic while others may be masked as “late-blooming” puberty. No estimates have been found on the prevalence of secondary hypogonadism; however, the Hypogonadism in Males study estimated the overall (primary and secondary) prevalence of hypogonadism (total T < 300 ng/dL) in 2,162 men aged 45 years and older to be 38.7% [11].

The goal of testosterone replacement therapy (TRT) is to achieve normal physiological testosterone levels while minimizing adverse effects and using the most convenient route of administration possible for the patient [12]. Current treatments for hypogonadism in the United States have significant disadvantages due to their route of administration that may reduce the number of individuals receiving treatment, failure to achieve physiologically normal patterns of circulating T, or possibly result in the accidental exposure of other individuals to T [13]. Regular intramuscular injections are unattractive for some patients due to injection site pain and the necessity of regular visits to physician offices. Topical T

formulations have been the recent subject of a Food and Drug Administration (FDA) requirement for a "black box" warning in the US. The warning came in response to accidental contact of children with male adults (typically family) who had applied the formulations, resulting in elevated T levels in the children and abnormal growth of genitalia [14].

To overcome these treatment disadvantages, Marius Pharmaceuticals is developing a novel, oral formulation of testosterone undecanoate (TU), SOV2012-F1, for the treatment of primary and secondary hypogonadism. A T pro-drug, TU is available in Europe and Canada for oral TRT in adult men for conditions associated with a deficiency or absence of endogenous T [15]. Brand names associated with this formulation include Andriol™ and Andriol Testocaps™, depending on the market. However, this product is reported to have an unpredictable absorption pattern, resulting in short-lived peaks in T levels after ingestion [15,16,17,18].

The Marius Pharmaceuticals formulation (selected from 10 formulations studied) contains TU, common pharmaceutical excipients, and phytosterol esters in soft-gelatin capsules. In the US, phytosterols, phytostanols, and their esters have received Generally Recognized as Safe status. Phytosterols are hypothesized to improve lymphatic absorption of TU. The addition of phytosterol esters to lipid-based formulations enhances the solubility of TU in this formulation. These T esters, much more so than T alone, are recognized by the small intestine as fat. Thus, most of the oral TU dose is absorbed via intestinal lymphatics, potentially avoiding first-pass hepatic metabolism. Absorption via the lymphatic system is enhanced by the consumption of a meal before dosing. In dog pharmacokinetic (PK) studies, co-dosing of phytosterols enhanced T exposure relative to a reference formulation having the same composition as Andriol Testocaps [19]. Additional nonclinical studies conducted by Marius Pharmaceuticals following a September 16, 2013 pre-Investigational New Drug Application meeting support the safety of TU when administered as SOV2012-F1. The nonclinical studies included *in vitro* binding studies to the human androgen and estrogen receptors, *in vivo* absorption, distribution, metabolism, and excretion/PK study in rats, rat male fertility study, and a 90-day dog repeat-dose toxicology study.

Side effects associated with various T formulations in clinical trials include application site reactions (up to 37% with transdermal formulations), acne (1% to 8%), depression (1% to 3%), prostate abnormalities (1% to 5%), gynecomastia (1% to 3%), and headache (1% to 4%). Adverse events (AEs) with TRT have been discussed in the literature and include: cardiovascular disease, lipid alterations, erythrocytosis, polycythemia, benign prostatic hypertrophy, prostate cancer, hepatotoxicity (associated with oral alkylated agents), and peripheral edema. All current T preparations have the potential of stimulating prostate gland growth and possibly prostate cancer [19].

Five PK studies in hypogonadal men demonstrate that single and repeat doses of TU up to 500 mg twice daily (316 mg T equivalents) are well tolerated with minimal AEs [19]. In addition, several human studies have been published on the use of oral TU as TRT [20,21,22]. In these studies, single doses up to 800 mg and repeat doses of 300 mg and 400 mg TU 3 times and 2 times a day, respectively, were well-tolerated with minimal side effects.

The Phase 2b clinical study, Study SOV-TU-PK2013 [23], was designed to select a starting dose for Phase 3 and develop an algorithm for adjusting SOV2012-F1 doses that maximized the percentage of subjects with maximum concentration (C_{max}) and 24-hour T levels within FDA guidelines [13]. Additional assessments included the effect of the composition of food on the PK of T, dihydrotestosterone (DHT), TU, and dihydrotestosterone undecanoate (DHTU), and a comparison of different aspects of the bioanalytical sample collection methods. Consumption of meals of 15%, 30%, and 50 calories from fat progressively increased the exposure of T and DHT, consistent with published studies showing the importance of fat to the absorption of TU [18].

Results of the nonclinical studies in combination with the Phase 2b data support progression to the proposed Phase 3 study in approximately 300 hypogonadal men. This randomized, 365-day, open-label, active-controlled study will include a 90-day efficacy period followed by a 9-month safety evaluation period comparing SOV2012-F1 taken with food with AndroGel® 1.62% applied once daily (QD). Both treatments will be continued for the 12- month duration of the study, and the comparator will be used only for assessment of safety. Doses of both SOV2012-F1 and AndroGel will be titrated according to the algorithms documented in this protocol. Subjects will not be asked to change their eating habits. In a rare autosomal-recessive condition, phytosterolemia, caused by a defect in a gut protein that transports phytosterols into the intestinal lumen, plant-derived sterols accumulate to high levels in blood and tissues. These patients can develop adrenal insufficiency (Reference: Mushtaq T et al., Adrenal insufficiency in phytosterolaemia. Eur J Endocrinol 157:S61-5, 2007). To rule out any effect of the phytosterols in SOV2012-F1 on adrenal function, ACTH stimulation testing will be done in a subset of subjects at baseline and at the end of the study.

5.2. Study Rationale

SOV2012-F1 is a novel oral preparation of TU and has demonstrated a favorable PK and tolerability profile in studies to date. This Phase 3 study is intended to provide sufficient data to demonstrate efficacy and safety, and to form the basis for a reviewable New Drug Application for the male hypogonadism indication.

This Phase 3 study, with a 90-day efficacy period and 9-month safety evaluation period, is designed to determine the efficacy of oral SOV2012-F1 as measured by the percentage of subjects with male hypogonadism with average plasma total testosterone (T Cavg) within the normal range after 90 days of treatment. The study will have shown effectiveness of SOV2012-F1 if ≥ 75% of the Full Analysis Set population has plasma T Cavg within the normal range after 90 days, with the lower bound of the 95% confidence interval (CI) ≥ 65%.

The secondary objective of the study is to determine the percentage of SOV2012-F1–treated subjects who have a maximum plasma testosterone concentration (T Cmax) within FDA- defined limits after 90 days of treatment.

Testosterone measurements in subjects receiving SOV2012-F1, which contains TU (a prodrug of T) will be made using plasma samples. The sampling tubes contain an enzyme

inhibitor to prevent post-blood collection conversion of TU to T. Measurements of T for AndroGel are made using serum samples, as per product information [1, Section 16.4].

Exploratory objectives are (1) to determine change from baseline in outcomes reported by SOV2012-F1–treated and AndroGel-treated subjects in International Prostate Symptom Score (IPSS; Section 16.5), Psychosexual Daily Questionnaire (PDQ; Section 16.6), Short Form Survey (SF-36; Section 16.7), and International Index of Erectile Function (IIEF; Section 16.8) after 52 weeks of treatment; and (2) to determine change from baseline in fasting serum glucose and fasting insulin concentrations in SOV2012-F1–treated and AndroGel-treated subjects after 52 weeks of treatment. The second exploratory objective is based on research showing that among older men, higher levels of DHT are inversely associated with insulin resistance and risk of having/developing diabetes mellitus [24]. An additional exploratory objective is the assessment of bioanalytical sample stability for subjects on SOV2012-F1 oral TU.

Safety objectives are:

(1) to determine the incidence of AEs, serious adverse events (SAEs), and AEs leading to study withdrawal in SOV2012-F1–treated subjects compared with AndroGel-treated subjects after 52 weeks of treatment;

(2) to assess change from baseline in blood pressure (BP), liver function tests, hematology parameters, hormone levels, lipid profiles, and serum prostate- specific antigen (PSA) in SOV2012-F1–treated and AndroGel-treated subjects after 52 weeks of treatment. Blood pressure measurements will be taken at screening and each study visit, including at 4-hour intervals over the 24-hour period of PK collection visits. Blood pressure measurements on all study visit days will be duplicated within 5 minutes. If the difference in systolic blood pressure (sBP) and diastolic blood pressure (dBP) measurements is > 10 mm Hg and > 5 mm Hg, respectively, a third BP measurement will be taken and results averaged;

(3) to determine the effect of SOV2012-F1 on adrenal cortical function, the cortisol response to synthetic ACTH will be measured at baseline and after 52 weeks of treatment in a subset of 30 subjects. At randomization, 45 patients (2:1 ratio of SOV2012-F1 to AndroGel subjects) will be enrolled to ensure 30 subjects are available for assessment at the End of Treatment (Day 365).

An artefact in hematocrit measurement due to the use of a central laboratory and the consequent delay in sample evaluation has led to the use of hemoglobin (Hgb) instead of hematocrit as an exclusion criterion and for hematology-related safety endpoints.

The absorption of TU depends upon meal ingestion. Absorption is also proportional to the fat content of a meal. Subjects in the study are expected to maintain their normal diet. A study of optimum dose timing demonstrated that ingestion of the SOV2012-F1 formulation after a meal resulted in increased absorption, hence in this study subjects in the SOV2012-F1 study arm should take their morning and evening doses 30 minutes after the beginning of breakfast and dinner, respectively. This dose timing has been used in previous clinical studies of the SOV2012-F1 formulation.

National dietary data show average 24-hour energy intake for males aged 19 years or more is 2514 kcal/day, with men in the 90th percentile consuming 3434 calories daily [25]. Researchers using dietary intake data from the National Health and Nutrition Examination Surveys found the average 24-hour energy (2586 kcals) distribution by meal for adult men is 508 kcals (19.6%) at breakfast, 544 kcals (21.0%) at lunch, 919 kcals (35.5%) at dinner, and 615 kcals (23.8%) as snacks [26, 27]. These data suggest American men consume approximately the same number of calories at breakfast and lunch, while consuming considerably more calories during the dinner meal. These amounts and distributions of caloric intake versus meal have been used in designing menus for use on the 24-hour PK days (Visits 4, 6 and 8). The caloric amounts of meals and average fat content of meals provided for each subject on the PK days will be set using the data obtained from the ASA24 diet recall system for each subject.

6. STUDY OBJECTIVES

6.1. Primary Objective

The primary objective of the study is to determine the efficacy of oral SOV2012-F1 as measured by the percentage of male hypogonadal subjects with plasma T C_{avg} within the normal range after 90 days of treatment.

6.2. Secondary Objective

The secondary objective of the study is to determine the percentage of

SOV2012-F1–treated subjects with plasma T C_{max} values (a) < 1500 ng/dL; (b) 1800 to 2500 ng/dL; and (c) > 2500 ng/dL after 90 days of treatment.

6.3. Exploratory Objectives

The exploratory objectives of the study are:

- To determine the change from baseline in the following subject-reported outcomes by SOV2012-F1–treated and AndroGel-treated subjects in I-PSS, PDQ, SF-36, and IIEF after 52 weeks of treatment.
- To determine change from baseline in fasting serum glucose and fasting insulin concentrations in SOV2012-F1–treated and AndroGel-treated subjects after 52 weeks of treatment.
- Assessment of bioanalytical sample stability for measurement of T and DHT in serum and plasma samples from subjects receiving TU orally, including three types of plasma tubes (EDTA, NaF/EDTA, and lithium heparin).

6.4. Safety Objectives

- To determine the incidence of AEs, SAEs, and AEs leading to study withdrawal in SOV2012-F1–treated subjects compared with AndroGel-treated subjects after 52 weeks of treatment.

- To assess change from baseline in BP, liver function tests, hematology parameters, hormone levels, lipid profiles, and serum prostate-specific antigen (PSA) in SOV2012-F1–treated and AndroGel-treated subjects after 52 weeks of treatment.
- To determine the effect of SOV2012-F1 on adrenal cortical function as assessed by measuring the cortisol response to synthetic ACTH at baseline and after 52 weeks of treatment in a subset of 30 SOV2012-F1 subjects and 15 AndroGel subjects.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan: Description

This will be a randomized, multicenter, open-label, active-controlled, efficacy (based on T C_{avg} and T C_{max}), and safety study in adult hypogonadal men. The study duration is 12 months (365 days), including a 90-day, open-label efficacy period and a 9-month

(275-day) safety evaluation period. All study visit days should be understood to be ±2 days (i.e., Visit 4, Day 14 may occur from Day 12 of the study period to Day 16) up through Visit 7, and ±3 days for Visit 8 (day 90) through End of Study (day 365).

Acceptable ranges for each visit are designated in the Schedule of Assessments (Table 7-1), Overall Study Design figures (Figure 7-1 and Figure 7-2), and Timing of Study Procedures (Section 8), but generally not designated throughout the text of this protocol.

Enrollment into the study will be based on selection criteria designed to reflect the general population of hypogonadal men. Subjects must be naïve to androgen replacement therapy or washed out adequately of prior androgen replacement therapies.

Subjects will undergo 2 screening visits (Screening Visit 1 and Screening Visit 2) during the study screening period to verify inclusion and exclusion criteria. Subjects must have 2 consecutive serum total T levels ≤ 281 ng/dL based on a blood sample drawn at least 3 days apart and obtained from 7 a.m. to 10 a.m. Furthermore, subjects must have at least 1 clinical feature consistent with male hypogonadism. A description of symptoms and signs consistent with male hypogonadism is provided in Section 7.3.2.

Eligible subjects will be randomized 2:1 (approximately 200 SOV2012-F1–treated subjects to 100 AndroGel-treated subjects, respectively) and stratified by study center to receive SOV2012-F1 with morning and evening meals, or AndroGel, a commonly prescribed topical T replacement product. Both treatments will be continued for the

12-month study duration, and the comparator (AndroGel) will be used only for assessment of safety.

Testosterone measurements in subjects receiving SOV2012-F1, which contains TU (a T prodrug), will be made using plasma samples. The sampling tubes contain an enzyme inhibitor to prevent post-blood collection conversion of TU to T. Measurements of T for AndroGel will be made using serum samples, as per product information.

SOV2012-F1 will be started at a total daily dose of 600 mg (400 mg with the morning meal and 200 mg with the evening meal). The plasma T concentration between 3 to 5 hours at Visit 4, Day 14 and Visit 6, Day 42 will determine the need, if any, to adjust the dose up or down by 200 mg at Visit 5, Day 28 and Visit 7, Day 56, respectively. The minimum dose of SOV2012-F1 will be 200 mg with the morning meal and no evening dose. The maximum dose of SOV2012-F1 will be 1000 mg (600 mg with the morning meal and 400 mg with the evening meal).

AndroGel will be applied at a starting dose of 40.5 mg QD. The serum T predose concentration (T $C_{predose}$) from a single blood draw at Day 14 and Day 42 will determine the need, if any, to titrate per the product information [2, Section16.4] at Day 28 and Day 56, respectively.

The final doses established in the efficacy period for SOV2012-F1 and AndroGel will be used at the start of the 9-month safety evaluation period. The dose of SOV2012-F1 may be up- or down-titrated on Day 180 and Day 270 based on the plasma T concentration from a single blood draw within 3 to 5 hours after the morning dose (Day 166 and Day 256). Single blood draw serum T concentrations predose at Day 166 and Day 256 will be used for AndroGel dose titration at Day 180 and Day 270, respectively, per product information.

If analysis of the Day 90 24-hour PK data reveals that a subject is on an incorrect dose, discontinuation of the subject may be appropriate in the following instances:

- A SOV2012-F1–treated subject has been previously down-titrated to 200 mg in the morning only, and T C_{max} is > 2500 ng/dL on Day 90: the subject will be discontinued, as continuation in the study will expose the subject to repeated T C_{max} values > 2500 ng/dL.
- A SOV2012-F1–treated subject has been up-titrated to 1000 mg, and T C_{avg} is below the normal range on Day 90: the subject may be discontinued if, in the opinion of the investigator, continuation in the study would expose the subject to an investigational treatment without probability of successful treatment.
- If a SOV2012-F1–treated subject has T C_{avg} below the normal range (2.5% percentile) on Day 90 the subject may be dose-titrated at an unscheduled visit, if the efficacy period data suggests benefit to the subject and an acceptable safety profile.

Discontinued subjects will be asked to complete the procedures of an End of Treatment Visit (see Section 8.3.10).

Titration decisions will be communicated through Interactive Web Response Technology (IWRT).

For more information on the dose-titration algorithms to be used in this study, see Section 7.4.7, Figure 7-1, and Figure 7-2.

Bioanalytical Sample Stability Substudy Investigational Plan

The Bioanalytical Sample Stability substudy is designed to assess the stability of T levels in samples obtained from subjects on oral TU dosing. The prodrug TU converts to T in blood samples ex-vivo due to the action of esterases. This substudy assesses the stability

of the sample as a function of sample type (serum or plasma), plasma tube type (EDTA, NaF/EDTA, lithium heparin), processing time, and processing temperature. To maximize the TU concentration, the samples will be obtained near TU Tmax, beginning 3 to 3.5 hours after dosing. Dosing will occur 30 minutes after beginning a high-fat breakfast of at least 700 kcals. Subjects enrolled in the bioanalytical substudy may participate at either V10 (Day 180) or V12 (Day 270), or at an unscheduled visit within a week of either visit and will be based on the date of subject informed consent.

7.1.1. Diet

The study meals designed for this research reflect average caloric and dietary fat intake patterns of adult American males. Since many of the 35 clinical sites for this study lack food preparation facilities, the study meals are commercially available, ready-to-eat microwavable meals. Meals were selected to deliver calorie and fat loads that mimic the subject's normal eating patterns established as described in the following paragraphs.

The study menus provide food choices for breakfast, lunch and dinner during the 24-hour clinic stay. The breakfast and dinner meals are designed to deliver varying percentages of calories from fat: low-fat meals (15-20%), moderate-fat meals (30- 35%), and high-fat meals (40-45%). All lunches are normal fat as no drug is administered with lunch.

For 24-hour PK collection visits, subjects will be dosed and fed in the clinic and will remain until after the final PK or safety assessment. SOV2012-F1–treated subjects will be confined to the clinic on Day 14 to Day 15, Day 42 to Day 43, and Day 90 to Day 91, for Visit 4, Visit 6, and Visit 8, respectively. AndroGel-treated subjects will be confined to the clinic only from Day 90 to Day 91, Visit 8. Subjects will be provided with breakfast at all visits that require fasted blood draws, and breakfast, lunch, and dinner during 24-hour PK collection visits.

Subjects may be offered breakfast at the end of the 24-hour PK visits after final PK or safety assessment. Subjects on SOV2012-F1 will take their morning dose 30 minutes after starting the breakfast. Breakfast and dinner meals provided with dosing will be consistent with their standard eating habits.

Subjects may be offered breakfast at the end of the 24-hour PK visits after final PK or safety assessment. Subjects on SOV2012-F1 will take their morning dose 30 (±5) minutes after starting the breakfast, as required by protocol.

The Automated Self-Administered 24-Hour Recall (ASA24) system, developed by the National Institutes of Health, has been found to be an effective and reliable tool for gathering high-quality dietary intake information [2,3].

At Screening Visit 1, all subjects will receive a meal diary to record three days of breakfasts and dinners prior to Visit 2. At Visit 2, the study coordinator at each site will enter the diary- recorded meals in to the ASA24 system in the presence of the subject for determining total calorie and fat intake for each meal type. Based on the results, subjects will be assigned at visit 3 to 1 of 3 meal categories for breakfast and dinner:

- low-fat meals ($\leq$ 20% calories from fat),
- normal-fat meals (>20% to 35% calories from fat),

- high-fat meals (>35% calories from fat).

The SOV2012-F1 study medication should be taken 30 (±5) minutes after the beginning of the breakfast and evening meals. Meal time should last approximately 30 (±5) minutes and then compliance assessed. Subjects in the SOV2012-F1 study arm will receive breakfast and dinner on Days 14, 42, and 90 in the clinic according to the meal categories based on the ASA24 system report. If the average reported fat content for a given meal is ≤ 20%, subjects will receive low-fat meals; if > 20% to ≤ 35%, subjects will receive normal-fat meals; and if > 35%, subjects will receive high-fat meals. Assignments are per meal type (e.g., a subject may receive a breakfast with different fat content than dinner, depending on his recorded eating patterns). All lunches will be normal fat. Meals provided to SOV2012-F1 subjects will contain enough volume to mimic their total average Kcals recorded in their food diary for breakfast and for dinner. Subjects will be provided light snacks, upon their request, in the afternoon and after dinner as long as it is 2 hours before or after the dosing meal, in order to minimize the effect on subjects completing their meals fully at the relevant dosing meals. For the SOV2012-F1 arm, subject's meals, meal fat content, and the percentage of meal consumed (0, 25%, 50%, 75%, 100%) will be recorded in the subject's electronic case report form (eCRF).

All subjects will receive breakfast at Visit 3, Day 1. Because there is no PK measurement after the first dose, subjects may choose from any breakfast offered by the site. Subjects will receive assigned breakfast on all other days they visit the clinic fasted for a blood draw.

AndroGel-treated subjects, who attend a clinic visit in a fasted state or at the confined Day 90 to Day 91 visit for 24-hour PK sampling, may receive any normal fat menu selection for their meals.

Additional meal and food intake procedures are described in Section 7.1.3, Schedule of Assessments, and Section 8, Timing of Study Procedures.

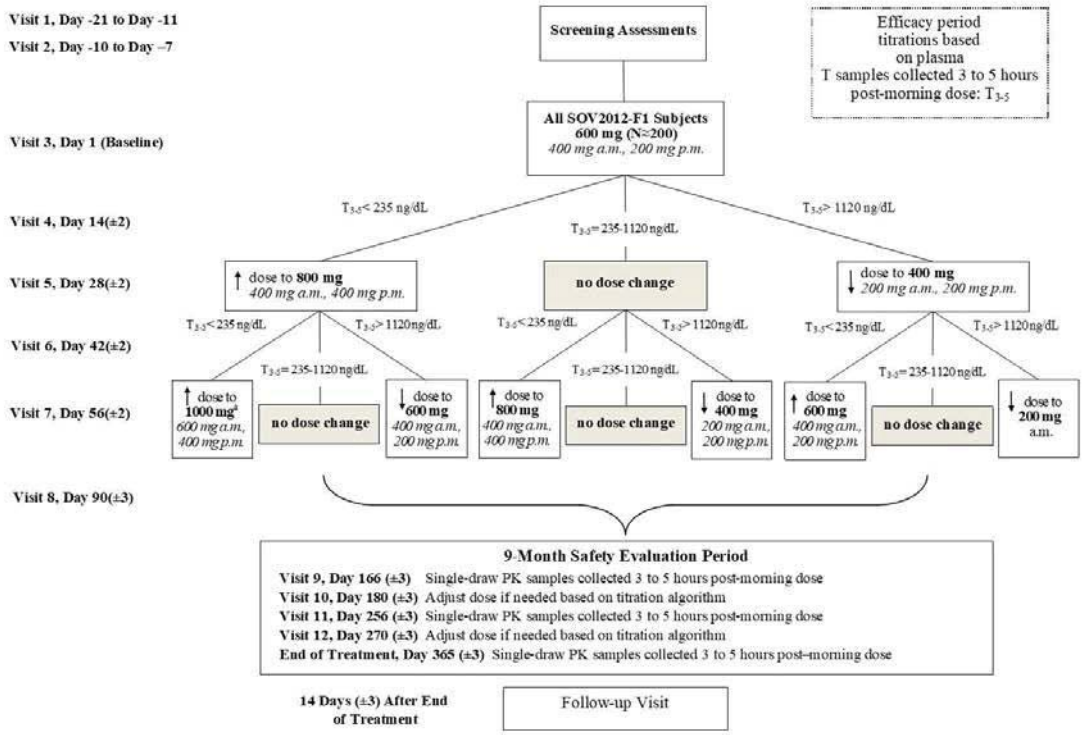
For Bioanalytical Sample Stability Substudy Only: SOV2012-F1 subjects participating in the bioanalytical sample stability substudy will receive a high-fat breakfast of at least

700kcals on the day of sampling (either Day 180 or Day 270, or at an unscheduled visit within a week of either visit). High-fat breakfast selections should be made from the MRS-TU-2019 study menu, and a minimum of 700 kcal provided.

7.1.2. Study Design

The overall study design for the SOV2012-F1 group is presented in Figure 7-1. The overall study design for the AndroGel group is presented in Figure 7-2.

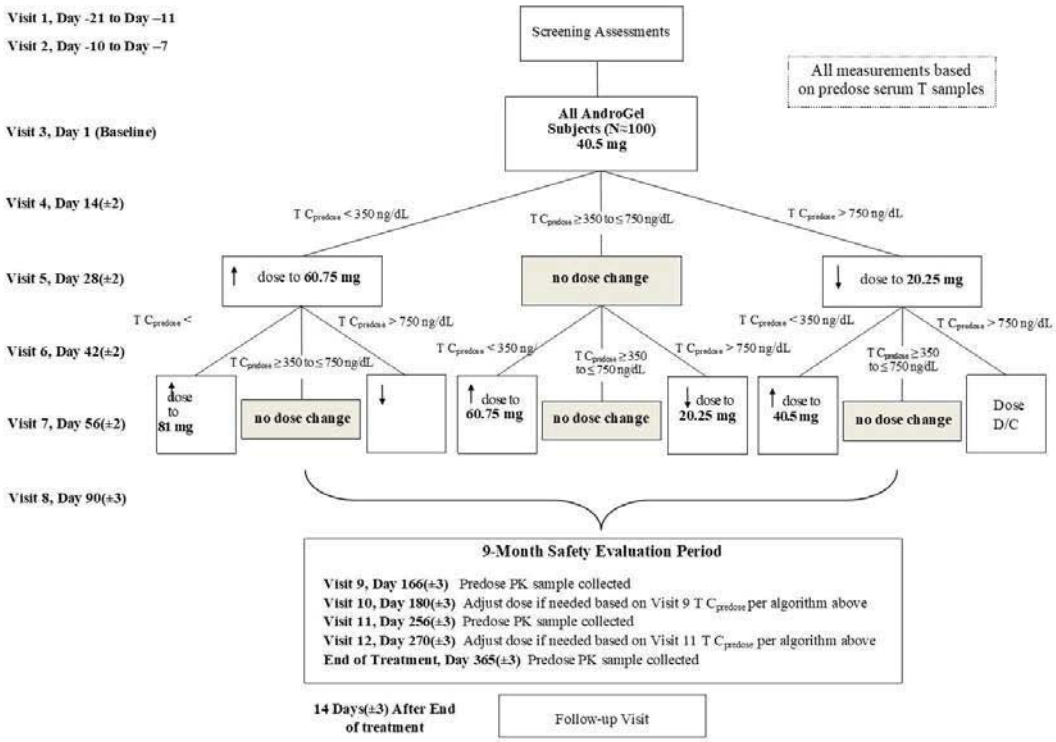
Figure 7-1 MRS-TU-2019 Overall Study Design, SOV2012-F1 Group (Main Study)



Abbreviations: a m. = morning; N = number of subjects; p m. = evening; T_{3-5} = plasma testosterone concentration measured between 3 and 5 hours (+10 min) post-morning dose.

[a] The investigator and the sponsor will review the data for each individual, and the reason for not responding to treatment will be investigated. Assuming correct compliance with study drug, SOV2012-F1 may be increased to 600 mg a m., 400 mg p m. at the investigator's discretion, taking safety into consideration, or
subjects may be discontinued from the study as non-responders. Data will be reported in the clinical study report.

Figure 7-2 MRS-TU-2019 Overall Study Design, AndroGel Group



Abbreviations: D/C = discontinued; N = number of subjects; T = testosterone; T $C_{predose}$ = serum testosterone predose concentration.

7.1.3. MRS-TU-2019 Schedule of Assessments

A Schedule of Assessments for MRS-TU-2019 is shown in Table 7-1, and study procedures are presented by study visit in Section 8.

For MRS-TU-2019EXT- Extension Study Schedule of Assessments, see Appendix 16.12

Table 7-1 MRS-TU-2019 Schedule of Assessments

Assessment	Pre-treatment		Treatment Period											Post-treatment
	Visit 1 Day -21 To Day -11	Visit 2 Day -10 to Day -7	Visit 3 Day 1 Baseline (within 10 days of Visit 2)[a]	Visit 4 Day 14 (+/-2)[b]	Visit 5 Day 28 (+/-2)	Visit 6 Day 42 (+/-2)[b]	Visit 7 Day 56 (+/-2)	Visit 8 Day 90 (+/-3)[a]	Visit 9 Day166 (+/-3)	Visit 10 Day 180 (+/-3)[a] ♣	Visit 11 Day 256 (+/-3)	Visit 12 Day 270 (+/-3) ♣	End of Treatment Day 365 (+/-3)[a,*] Early Withdrawal	Follow Up (14 days [+/-3] After Last Dose)
Informed consent	X									X ♣		X ♣		
Inclusion/exclusion criteria	X	X	X							X ♣		X ♣		
Randomization			X											
Demographic data	X													
Medical history	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[c]		X	X	X	X	X	X	X	X	X	X	X	X	
Height		X												
Vital signs[d]		X	X	X	X	X	X	X	X	X	X	X	X	
ECG		X												
Urinalysis[e]		X												
Urine drug screen[f]		X												
HIV, hepatitis screens		X												
Biochemistry[g]		X		X		X		X		X		X	X	
Endocrinology[h]		X						X					X	
Hematology[i]		X						X		X		X	X	
Total testosterone, serum, screening, all	X[j]	X[j]												
Fasting insulin			X	X		X		X		X		X	X[x]	
Lipid panel (TC, LDL, HDL, TGs)		X[z]		X		X		X		X		X	X	
PSA		X						X		X		X	X	
ACTH stimulation testing[y]			X[y]										X[y]	

Table continues on next page.

Assessment	Pre-treatment Screening		Treatment Period											Post-treatment
	Visit 1 Day -21 to Day -11	Visit 2 Day -10 to Day -7	Visit 3 Day 1 Baseline (within 10 days of Visit 2)[a]	Visit 4 Day 14 (+/-2)[b]	Visit 5 Day 28 (+/-2)	Visit 6 Day 42 (+/-2)[b]	Visit 7 Day 56 (+/-2)	Visit 8 Day 90 (+/-3)[a]	Visit 9 Day 166 (+/-3)	Visit 10 Day 180 (+/-3)[a, ♣]	Visit 11 Day 256 (+/-3)	Visit 12 Day 270 (+/-3)[a, ♣]	End of Treatment Day 365 (+/-3) or Early Withdrawal	Follow Up (14 days [+/-3] after Last Dose))
24-hour PK sampling, SOV2012-F1 group, plasma T, DHT				X[k]		X[k]		X[k,]						
24-hour PK sampling, SOV2012-F1 group, plasma TU, DHTU								X[l]						
Single-draw PK, SOV2012-F1 group, plasma T, DHT			X						X[m]		X[m]		X[m]	
24-hour PK sampling, AndroGel, serum T, DHT								X[n]						
Single-draw PK, AndroGel group, serum T, DHT			X	X		X			X[o]		X[o]		X[o]	
Blood draw for bioanalytical stability										X♣		X♣		
E2 (Single or 24-hour PK), SOV2012-F1 and AndroGel groups[p]			X					X						
Dose adjustments[q]					X		X			X		X		
I-PSS		X						X					X	
PDQ dispense		X					X		X		X	X		
PDQ collect			X					X		X		X	X	
IIEF			X					X	X		X		X	
SF-36			X					X					X	
ASA24 training[r]	X													
Provide Patient Food Diary	X													
Collect Food Diary and enter into ASA24		X												

Table continues on next page.

Breakfast served			X	X[s]		X[s]				X[♣]		X[♣]	X	
All meals served, SOV2012-F1 group[t]				X		X		X						
All meals served, AndroGel group[u]								X						
Adverse event reporting		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study medications			X[v]		X		X	X		X		X		
Perform accountability check[w]					X		X	X		X		X	X	

Abbreviations: ACTH = adrenocorticotropic hormone; ALT = alanine aminotransferase; ASA24 = Automated Self-Administered 24-Hour Recall; AST = aspartate aminotransferase;
ALP = alkaline phosphatase; BP = blood pressure; BUN = blood urea nitrogen; DHT = dihydrotestosterone; DHTU = dihydrotestosterone undecanoate; dBP = diastolic blood pressure; E2 = estradiol; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HbA1c = glycosylated hemoglobin; HDL = high-density lipoproteins; HIV = human immunodeficiency virus; IIEF = International Index of Erectile Function; I-PSS = International Prostate Symptom Score; LC-MS = liquid chromatography-mass spectrometry; LDH = lactate dehydrogenase; LDL = low-density lipoproteins; LH = luteinizing hormone; PDQ = Psychosexual Daily Questionnaire; PK = pharmacokinetic; PSA = prostate-specific antigen; sBP = systolic blood pressure; SF-36 = Short Form Survey; SHBG = sex hormone-binding globulin; T = testosterone; TC = total cholesterol; TGs = triglycerides; TSH = thyroid-stimulating hormone; WBC = white blood cells.
Note: Subjects come to the clinic for study procedures from 7 a m. to 10 a m. except for SOV2012-F1–treated subjects on Day 166 and Day 256, when they will arrive at the clinic in time for a single blood draw within 3 to 5 hours after the morning dose.
a All subjects come to the clinic having fasted for at least 8 hours. Subjects should remain well hydrated during fasting and drink at least one glass of water (240 mL or 8 oz) prior to visit. Subjects should have completed 7-day PDQ questionnaire and all lab results should be available.
b SOV2012-F1–treated subjects come to the clinic having fasted for at least 8 hours. Subjects should remain well hydrated during fasting and drink at least one glass of water (240 mL or 8 oz) prior to visit.
c Full physical examination must include administering an I-PSS questionnaire, assessment for the presence of gynecomastia, and digital rectal examination at Screening Visit 2, Visit 8 (Day 90), and End of Treatment (Day 365). At all other visits, subjects should undergo a symptom-directed physical examination.
d Vital signs include BP, heart rate, temperature, and weight. Blood pressure will be measured using a cuff appropriate to the subject's arm size, in a standardized manner, i.e., after the subject has rested in the sitting position for at least 5 minutes. On all study visit days where BP is measured only once (V2) or pre-dose (V3, V5, V7, V9-V12, End of treatment for both SOV2012-F1 and AndroGel; V4 and V6 for AndroGel), BP measurement will be duplicated within 5 minutes. If the difference in 2 sBP and dBP measurements is > 10 mm Hg and > 5 mm Hg, respectively, a third BP measurement will be taken and results averaged. BP will be monitored at 4-hour intervals (0, 4, 8, 12, 16, 20, and 24 hours) over the 24-hour PK collection period on V4, V6, and V8 for SOV2012-F1–treated subjects and on V8 for AndroGel-treated subjects (±5 minutes for all timepoints). Other vital signs will be assessed at Time 0 only. The time-zero measurement of BP at V4, V6 and V8 may be taken up to 60 minutes prior to dosing.
e Urinalysis includes pH, glucose, ketones, blood, protein, microscopy, and specific gravity.
f Urine drug screen will include, cocaine, narcotics, benzodiazepines, tetrahydrocannabinol, barbiturates, and amphetamines.
g Biochemistry includes AST, ALP, ALT, total bilirubin, creatinine, BUN, eGFR, LDH, glucose, total protein, albumin, sodium, potassium, calcium, and phosphorus. h Endocrinology consists of LH, FSH, SHBG, and TSH.
i Hematology includes hemoglobin, hematocrit, WBC, and platelets.
j Subjects must have 2 consecutive serum total testosterone (T) levels ≤ 281 ng/dL based on a blood sample obtained from 7 a m. to 10 a m., drawn on separate days, at least 3 days apart. Furthermore, subjects must have at least 1 clinical feature consistent with male hypogonadism. At Visit 1, a sample for testosterone is collected. At Visit 2, the biochemistry sampling includes sample for testosterone.
k PK samples are collected pre-morning dose and 1.5, 3, 4, 5, 6, 8, 12, 13.5, 15, 16, 17, 18, 20, and 24 hours after a m. dose for SOV2012-F1–treated subjects (±5 minutes for all timepoints). PK samples include plasma T and DHT. The initial and 12-hr doses are administered 30 (±5) minutes after the start of breakfast and evening meals.

l PK samples are collected pre-morning dose and 1.5, 3, 4, 5, 6, 8, 12, 13.5, 15, 16, 17, 18, 20, and 24 hours after a.m. dose for SOV2012-F1–treated subjects (±5 minutes for all timepoints). PK samples include plasma TU and DHTU. The initial and 12-hr doses are administered 30 (±5) minutes after the start of breakfast and evening meals.
m PK samples on these days should be drawn after the morning dose for SOV2012-F1–treated subjects within 3-5 hours (+10min). PK samples include plasma T and DHT. For early withdrawal subjects, no PK sample is collected.
n On Day 90(±3), blood samples for serum T and DHT will be collected at predose and 2, 4, 8, 12, 16, 20, and 24 hours post dose for AndroGel-treated subjects.
o On visit days after Day 90, blood samples for AndroGel-treated subjects will be collected pre-dose for serum T and DHT. For early withdrawal subjects, no PK sample is collected. p E2 samples are collected on Day 1 (single draw predose only) and on Day 90 (pre-morning dose and 1.5, 3, 4, 5, 6, 8, 12, 13.5, 15, 16, 17, 18, 20, and 24 hours after
a m. dose) for
SOV2012-F1 group (±5 minutes for all timepoints). For the AndroGel group, E2 samples are collected on Day 1 (single draw predose only) and on Day 90, (pre-dose and 2, 4, 8, 12, 16, 20, and 24 hours post dose).
q Dose adjustments, if needed, will be made on these days.
r Study coordinators will receive instructions for using the ASA24 online assessment for recording food intake and participate in a practice session. Subjects will be instructed to complete 3 days of breakfast and dinner entries into a meal diary between visit 1 and visit 2. At visit 2, study coordinators will enter meal data into ASA24 system in the presence of the subject.
s Subjects will be provided with a standardized breakfast after testing and lab sample collection is complete. On Day 14 and Day 42, the AndroGel group will receive breakfast at clinic visit, while the SOV2012-F1 group will receive all meals at confinement visit.
t Provide meals based on SOV2012-F1–treated subjects' ASA24 records (all lunches are normal fat), and record meals, meal fat content, and the percentage of meal consumed (0, 25%, 50%, 75%, 100%).
u Three meals will be provided to AndroGel-treated subjects on Day 90 only (all normal fat), but meal consumption will not be recorded.
v SOV2012-F1–treated subjects will be observed taking their first dose (400 mg) 30 (±5) minutes after starting their meal at the clinic. AndroGel-treated subjects will be instructed at Visit 3, Day 1 to apply the gel topically in the morning to the shoulders and upper arms, starting at 2 pump actuations (40.5 mg), and observed applying their first dose.
w Perform an accountability check on any remaining study drug and empty study drug containers.
x For early withdrawal subjects, fasting Insulin is not collected.
y ACTH stimulation testing is performed as a substudy (45 subjects enrolled for 30 completers, 2:1 ratio between SOV2012-F1 and AndroGel™.)
z If LDL cannot be calculated, it should be measured directly to determine whether the subject satisfies inclusion criterion 5c. See Section 8.1.2 for further details.
♣Bioanalytical Sample Stability Substudy: On either V10 (Day 180) or V12 (Day 270), subjects provide consent. Subjects may also perform BSSS sampling at an unscheduled visit within one week of V10 or V12. Subjects are provided with high fat breakfast (minimum 700 kcal) following fasting lab draw. Subjects take their 400 mg SOV2012-F1 dose 30 (± 5) minutes after beginning the meal. The blood samples for the stability study are obtained beginning 3 to 3.5 hours (± 10 minutes) after dosing (samples will be drawn over a 30-45 min period; collection details provided in the central Laboratory Manual).
*MRS-TU-2019 EXT ABPM Extension Substudy: Please refer to Appendix 16.12 for Schedule of Assessments for subjects participating in the MRS-TU-2019 EXT study.

7.2. Discussion of Study Design

This randomized, multicenter, open-label, active-controlled, efficacy, and safety study in adult hypogonadal men is intended to support a New Drug Application for the male hypogonadism indication (see Section 5.2). The open-label design is appropriate because the endpoints are based on laboratory measurements. This design has become standard practice in Phase 3 TRT studies. The requirement for ingestion of oral TU medications with meals is necessary for good drug absorption.

A screening period of up to 21 days is followed by a 365-day study period, including a 90-day, open-label efficacy period and a 9-month (275-day) safety evaluation period that will allow for a full assessment of the safety and tolerability of SOV2012-F1 and AndroGel. During the efficacy period, plasma T C_{avg} and T C_{max} will be assessed to determine if the primary and secondary efficacy of SOV2012-F1 is consistent with FDA targets for regulatory approval of TRT products, as outlined in an Advisory Committee Industry Briefing Document [13].

The study requires three 24-hour PK collections for SOV2012-F1–treated subjects and one for AndroGel-treated subjects that will require overnight stays at the clinic during the first 90 days (Section 7.1). Dose-titration algorithms documented in this protocol will provide for dose adjustments (Section 7.4.5) during the efficacy and safety periods.

A dose-titration algorithm for adjustment of SOV2012-F1 dosing using single blood draw samples was developed based on the 24-hour PK profiles obtained during the 84-day Phase 2b clinical study. This single-dose titration algorithm will be used during the Phase 3 efficacy and safety periods.

For AndroGel, dose titration during the efficacy and safety periods will be per product information [1, Section 16.4].

Bioanalytical Sample Stability Substudy

The blood **samples for the sample stability study will be obtained after intake of a high-fat breakfast containing at least 700kcal, followed in 30min by morning dose. Sampling will begin 3 to 3.5 hours (± 10 minutes)** after dosing (samples will be drawn over a 30-45 min period; collection details are provided in the central Laboratory Manual).

Eligible subjects are only those on a dose level that includes a 400 mg SOV2012-F1 dose with the morning meal – this includes the 600 mg and 800 mg daily dose levels. The bioanalytical substudy samples will be obtained at approximately either Day 180 (Visit 10) or Day 270 (Visit 12) plus or minus one week, based on the date of signed informed consent, in at least 12 subjects.

The processing timepoints and conditions are provided below and will be detailed in the laboratory manual.

Tube	Processing Timepoints	Temperatures	Quantitation
Serum	15, 30, 60, 90, 120 (zero time does not apply)	Room temperature clotting, then stored at -20°C or lower.	LC-MS/MS
Plasma (EDTA)	0*, 15, 30, 60, 90, 120	Room temperature and ice/4°C, then stored at -20°C or lower.	
Plasma (NaF/EDTA)*			
Plasma (Li Heparin)			

*0 timepoint for Plasma NaF/EDTA will also be processed for TU

7.3. Selection of Study Population

7.3.1. Number of Planned Subjects

Approximately 1850 subjects are planned to be screened to enroll approximately 300 subjects at 35 sites in the United States. It is expected that there will be approximately 150 SOV2012-F1–treated subjects who complete the first 90 days of the study and more than 100 who will complete all 365 days. Refer to the statistical considerations on which the numbers are based in Section 10.12.

Bioanalytical Sample Stability Substudy

At least 12 subjects assigned to SOV2012-F1 in MRS-TU-2019, on a minimum AM dose of 400 mg (600 mg or 800 mg total daily dose), will be enrolled in the bioanalytical sample stability sub-study. Up to 15 subjects will be enrolled in the substudy. This provides sufficient data for assessment of the impact on sample stability of sample type, collection tube, processing time and temperature.

7.3.2. Inclusion Criteria

To be eligible for study entry, subjects must satisfy all of the following criteria:

1. Male aged 18 to 65 years, inclusive at the time of providing informed consent to participate in the study.
2. Hypogonadism defined as having 2 consecutive serum total T levels equal to or less than 281 ng/dL based on a blood sample, drawn at least 3 days apart, between 7 a.m. and 10 a.m.
3. At least 1 clinical feature consistent with male hypogonadism. If a subject is receiving commercial TRT prior to Screening Visit 1, he must have a history of at least 1 clinical feature consistent with male hypogonadism. Appendix 16.2
4. Must be naïve to androgen replacement therapy or washed out adequately of prior androgen replacement therapies; willing to cease current T treatment; or

currently not taking any T treatment. Subjects must remain off all forms of T, except for dispensed study drug, throughout the entire study.

5. No unstable ongoing concomitant medical conditions. Treated and well-controlled conditions such as type 2 diabetes, hypertension, or dyslipidemia are acceptable with stable medication in place for at least 3 months prior to study entry:
    a. Hemoglobin A1c < 8.0%
    b. BP < 150/90 mm Hg

        ***for newly enrolled subjects into MRS-TU-2019EXT, ABPM Extension Study,** in-clinic, average BP must be ≤ 140/90 at screening, for inclusion into the MRS-TU-2019EXT study.

    c. Low-density lipoprotein cholesterol < 190 mg/dL.
6. Subjects with an endocrine disorder other than hypogonadism requiring treatment must be on a stable dose of replacement medication for at least 3 months prior to study entry.
7. Adequate venous access to allow collection of a number of blood samples via a venous cannula.
8. Written informed consent to participate in the study and ability to comply with all study requirements.
9. **For Bioanalytical Sample Stability Substudy only**: Must be on SOV2012-F1 dose of at least 400 mg in AM (600 or 800 mg total daily dose) at time of consent.

7.3.3. Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criteria are applicable:

1. Serum PSA > 2.5 ng/ml and/or abnormal prostate gland on palpation, e.g., palpable nodes, at Screening Visit 2.
2. Received oral, topical, intranasal, or buccal T therapy within the previous 2 weeks, intramuscular T injection of short-acting duration within the previous 4 weeks, intramuscular T injection of long-acting duration within the previous 20 weeks, or T implantable pellets within the previous 6 months.

    ***For ABPM Extension Study Only: Newly Enrolled Subjects to MRS-TU-2019EXT ABPM Extension Study**, patients *must not have received prior testosterone replacement therapy within 8 weeks* of the start of the study, with the exception of T implantable pellets which are excluded for 6 months.
3. Use of any drug that could interfere with measurement or assessment of serum androgen levels, including 5 alpha-reductase inhibitors, anabolic steroids, and drugs with antiandrogenic properties (e.g., spironolactone, cimetidine, flutamide, bicalutamide, and ketoconazole). These drugs must be stopped for at least 1 month prior to study entry (6 months in the case of dutasteride). Patients taking potent, long-acting opiate therapy on a daily basis are not eligible for the study.

Conversely, ad hoc use of potent, short-acting opiates for a period of less than 7 days may be permitted after discussion with the Marius Pharmaceuticals medical monitor.

4. Use of over-the-counter products, including natural health products (e.g., food supplements and herbal supplements such as saw palmetto or phytoestrogens) that may affect total T levels, within 7 days prior to study entry.
5. History of drug or alcohol abuse within the past 2 years that in the opinion of the investigator could interfere with study participation and/or influence study efficacy and safety endpoints assessments.
6. Unstable or chronic disease that could interfere with participation in the study or patient safety, including psychiatric disorders.
7. Myocardial infarction, coronary artery surgery, heart failure, stroke, unstable angina, or other unstable cardiovascular disease within the past 6 months.
8. Abnormal ECG considered clinically significant by investigator at Screening.
9. Diagnosis of any cancer within the previous 5 years other than basal or squamous cell skin cancer with clear margins.
10. Any surgical or medical condition that might alter administration of the study drug or comparator, including history of gastric surgery, cholecystectomy, vagotomy, small bowel resection, or any surgical procedure or medications (e.g., GLP-1 agonists and motility agents such as domperidone, metoclopramide, etc.) that might interfere with gastrointestinal motility, pH, or absorption of TU.
11. Duodenal or gastric ulcers, or gastrointestinal/rectal bleeding during the 3 months prior to screening.
12. Chronic skin conditions on the chest or upper arms that would prevent administration of AndroGel in a manner designed to ensure reliable and consistent absorption thereof.
13. Human immunodeficiency virus (HIV) infection.
14. Chronic hepatitis B and/or hepatitis C virus infection (as determined by positive testing for hepatitis B virus surface antigen or antibody to hepatitis C virus [HCV] with confirmatory testing, i.e., detectable serum HCV ribonucleic acid [RNA]).
15. Clinically significant abnormal laboratory values at screening, including but not limited to:
    a. Elevated liver enzymes (aspartate aminotransferase [AST], aspartate aminotransferase [ALT] > 2X upper limit of normal
    b. Estimated glomerular filtration rate < 60 ml/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease formula
    c. Hemoglobin < 11.0 g/dL or > 16.0 g/dL. For a subject previously on testosterone replacement therapy with less than 30 days washout prior to screening Visit 2, hemoglobin < 11.0 g/dL or > 17.0 g/dL.

16. ~~Hematocrit > 48%. For subjects previously on testosterone replacement therapy with less than 30 days washout prior to screening visit 2, hematocrit > 50%~~
    NOTE: Exclusion criteria #16 removed with Version 5.0 of Protocol.

    Numbering retained for clarity of records.
17. Severe or untreated obstructive sleep apnea syndrome.
18. Severe lower urinary tract symptoms (American Urological Association/ I PSS ≥ 19).
19. History of any clinically significant illness, infection, or surgical procedure within 1 month prior to study entry.
20. Past, current, or suspected prostate or breast cancer.
21. History of long QT syndrome or unexplained sudden death in a first-degree relative (parent, sibling, or child).
22. Concurrent treatment with medications that may impact the absorption, distribution, metabolism, or excretion of TU or place the subject at risk for treatment with T.
23. Subject has a partner who is currently pregnant or planning pregnancy during the study.
24. Treatment with any other investigational drug within 30 days of study entry or > 5 half- lives (whichever is longer) and at any time during the study.
25. History of noncompliance to medical regimens or potential unreliability in the opinion of the investigator.
26. Unwilling or unable to comply to the dietary requirements for this study.
27. History of polycythemia, either idiopathic or associated with TRT use.
28. Donated blood (≥ 500 mL) within the 12-week period prior to study entry.
29. History of an abnormal bleeding tendency or thrombophlebitis within the previous 2 years that is not linked to venipuncture or intravenous cannulation.
30. Onset of gynecomastia within the previous 6 months.
31. **For ACTH Stimulation Substudy only:** Primary or secondary adrenal insufficiency.
32. **For Bioanalytical Sample Stability Substudy only**: hemoglobin less than 13 g/dL at most recent central laboratory assessment

7.4. Investigational Products

7.4.1. Investigational Products Administered

Eligible subjects will be randomized 2:1 and stratified by study center to receive oral TU (SOV2012-F1) or AndroGel. Both treatments will be continued for the 12-month study duration.

SOV2012-F1 will be provided in 200-mg capsules, with a starting total daily dose in the study of 600 mg (400 mg with morning meal, 200 mg with evening meal). Subjects will be instructed to take the SOV2012-F1 capsules with water 30 (±5) minutes after the start of their meal.

Subjects randomized to AndroGel will be instructed at Visit 3, Day 1 to apply the gel topically in the morning to the shoulders and upper arms, starting at 2 pump actuations (40.5 mg).

AndroGel is to be applied to clean, dry, intact skin of the shoulders and upper arms. It should not be applied to any other parts of the body including the abdomen, genitals, chest, armpits (axillae), or knees. See Warnings and Precautions, Section 9.1.3.1.1.

7.4.2. Identity of Investigational and Comparator Products

SOV2012-F1 contains TU a Self-Emulsifying Drug Delivery Systems formulation within a soft-gelatin capsule. SOV2012-F1 is available in three strengths: 100 mg TU, 150 mg TU and 200 mg TU per capsule. Based on the molecular weights of TU and T, 100 mg, 150 mg and 200 mg TU are equivalent to approximately 63, 95 and 126 mg of testosterone, respectively. SOV2012-F1 is to be stored at controlled room temperature 20° to 25°C (68° to 77°F), with excursions permitted to 15° to 30°C. The drug product will be manufactured by Procaps (Barranquilla, Colombia) and is packaged in HDPE bottles with induction-sealed closures and caps.

AndroGel is a clear, colorless gel containing 1.62% T, which is its active pharmacologic ingredient. AndroGel is to be stored at controlled room temperature 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C. The product is manufactured by AbbVie (North Chicago, Illinois).

All study drugs will be manufactured and imported according to the relevant regulatory requirements. All packaging and labelling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

7.4.3. Packaging and Labeling

The packaging and labelling of SOV2012-F1 will be performed by Procaps (Barranquilla, Colombia). All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements. SOV2012-F1 capsules will be packaged in a high-density polyethylene safety bottle.

In its 1.62% T formulation, AndroGel will be supplied in non-aerosol, metered-dose pumps that deliver 20.25 mg of T per complete pump actuation. The pumps are composed of plastic and stainless steel and a low-density polyethylene/aluminum foil inner liner encased in rigid plastic with a polypropylene cap. Each 88-g, metered-dose pump is capable of dispensing 75 g of gel or 60 metered pump actuations; each pump actuation dispenses 1.25 g of gel.

7.4.4. Method of Assigning Subjects to Treatment Groups

Eligible subjects will be randomized 2:1 (approximately 200 SOV2012-F1–treated subjects to 100 AndroGel-treated subjects, respectively) using an interactive web randomization system and stratified by study center to receive SOV2012-F1 or AndroGel.

7.4.5. Starting Doses in the Study

Based on the results from the completed Phase 2b study (Study SOV-TU-PK2013) [23], Marius Pharmaceuticals has selected 600 mg as the starting dose (400 mg with morning meal, 200 mg with evening meal). The dose will be adjusted up or down, if needed, based on the dose-titration procedures described in Section 7.4.7.

AndroGel will be applied at a starting dose of 40.5 mg QD in the morning and titrated per product information [1, Section 16.4].

7.4.6. Administration of SOV2012-F1 Drug

The SOV2012-F1 drug product is to be taken with water with meals. The dose should be taken about 30 (±5) minutes after start of the meal. It should not be taken before or at the start of a meal.

7.4.7. Dose Titration

The dose of study drug will be titrated during the efficacy period using an algorithm that was developed using 24-hr PK data obtained from the 84-day Phase 2b study of SOV2012-F1 in 36 subjects, and serum T $C_{predose}$ for AndroGel, per product information. The final dose established in the 90-day efficacy period for SOV2012-F1 will be used at the start of the 9-month safety evaluation period, and the dose may be up- or down-titrated on Days 180 and 270 based on the plasma T concentration from a single blood draw within 3 to 5 hours after dosing (Day 166 and Day 256). Subjects on AndroGel may be up- or down-titrated on Day 180 and Day 270 based on single-draw serum T Cpredose levels at Day 166 and Day 256, per product information.

Dose reduction will also occur for safety based on hemoglobin levels >18 g/dL nominally measured at Visits 8, 10 and 12 during the study. See Section 9.1.3.1.2 Hematology for the dose titration schedule due to hemoglobin levels > 18 g/dL.

7.4.7.1. SOV2012-F1 Group

Dose titration for each subject will be based on the plasma T measured between 3 to 5 hours (±10 min) after the morning dose at Day 14 and Day 42. Dose titrations will occur at Day 28 and Day 56 if needed, based on the following algorithm:

- For subjects who may need dose titration at Day 28 based on the plasma T level obtained between 3 to 5 hours on Day 14:
    - $T_{3\text{-}5} < 235$ ng/dL: dose increased to 800 mg (400 mg a.m., 400 mg p.m.)
    - $T_{3\text{-}5} \geq 235$ to ≤ 1120 ng/dL: no dose change
    - $T_{3\text{-}5} > 1120$ ng/dL: dose decreased to 400 mg (200 mg a.m., 200 mg p.m.)

- For subjects who may need dose titration at Day 56, based on the plasma T level obtained between 3 to 5 hours on Day 42:
    - For subjects whose dose was not titrated previously (i.e., remained at 400 mg a.m., 200 mg p.m.) and the resulting plasma T_{3-5} at Day 42 are:
        - $T_{3-5} < 235$ ng/dL: dose increased to 800 mg (400 mg a.m., 400 mg p.m.)
        - $T_{3-5} \geq 235$ to ≤ 1120 ng/dL: no dose change
        - $T_{3-5} > 1120$ ng/dL: dose decreased to 400 mg (200 mg a.m., 200 mg p.m.)
    - For subjects whose dose was previously decreased to 400 mg (200 mg a.m., 200 mg p.m.), and the resulting plasma T_{3-5} at Day 42 are:
        - $T_{3-5} < 235$ ng/dL: dose increased to 600 mg (400 mg a.m., 200 mg p.m.)
        - $T_{3-5} \geq 235$ to ≤ 1120 ng/dL: no dose change
        - $T_{3-5} > 1120$ ng/dL: dose may be further decreased to 200 mg a.m.
    - For subjects whose dose was previously increased to 800 mg (400 mg a.m., 400 mg p.m.), and the resulting plasma T_{3-5} at Day 42 are:
        - $T_{3-5} < 235$ ng/dL: The investigator and sponsor will review the data for each individual, and the reason for not responding to the treatment will be further investigated. Assuming correct compliance with the study drug, the dose may be increased to 1000 mg (600 mg a.m., 400 mg p.m.) at the investigator's discretion, taking safety into consideration, or subjects may be discontinued from the study as non- responders. Data will be reported in the clinical study report.
        - $T_{3-5} \geq 235$ to ≤ 1120 ng/dL: no dose change
        - $T_{3-5} > 1120$ ng/dL: dose decreased to 600 mg (400 mg a.m., 200 mg p.m.)

If analysis of the Day 90 24-hour PK data reveals that a subject is on an incorrect dose, discontinuation of the subject may be appropriate, as detailed in Section 7.1.

During the 9-month safety evaluation period, the dose may be up- or down-titrated on Days 180 and 270 using a single time point T measurement obtained 3 to 5 hours after the morning dose on Days 166, and 256, respectively.

A graphic representation of SOV2012-F1 dose titration in the study is provided in Figure 7-1.

7.4.7.2. AndroGel Group

The need for dose titration for each subject will be based on the serum T concentration from a single pre-dose blood draw (T $C_{predose}$) at Day 14 and Day 42. Dose titrations will occur on Day 28 and Day 56, if needed, based on the following algorithm:

- T $C_{predose}$ < 350 ng/dL: increase daily dose by 20.25 mg (1 additional pump actuation)
- T $C_{predose}$ ≥ 350 and ≤ 750 ng/dL: no dose change
- T $C_{predose}$ > 750 ng/dL: decrease daily dose by 20.25 mg (1 less pump actuation)

AndroGel-treated subjects whose dose was reduced to 20.25 mg at Day 28 and have a T $C_{predose}$ of > 750 ng/dL at Day 42 will be discontinued from the study.

During the 9-month safety evaluation period, Day 166 and Day 256 single-draw serum T $C_{predose}$ levels will be used for dose titration on Day 180 and Day 270, respectively, per product information.

A graphic representation of AndroGel dose titration in the study is presented in Figure 7.2.

7.4.8. Blinding

Not applicable. This is an open-label study.

7.4.9. Prior and Concomitant Therapy

If any medication or nutritional supplement is taken prior to screening or during the screening phase, the name, dose, route, frequency of dosing, start and stop dates, and reason for use will be recorded on the concomitant medication page in the eCRF. Subjects will be asked about their treatment history for hypogonadism and the start and stop dates for their most recent TRT at Screening Visit 1. Concomitant medications will be recorded at each study visit. Any concomitant procedure or intervention should be recorded on the eCRF concomitant medication page as well.

7.4.9.1. Prohibited Medication/Therapy

Subjects must be washed out of and not use any forms of T except for study drug throughout the entire study. This includes oral, topical, intranasal, or buccal T therapy within the previous 2 weeks, intramuscular T injection of short-acting duration within the previous 4 weeks, intramuscular T injection of long-acting duration within the previous 20 weeks, or T implantable pellets within the previous 6 months.

In addition, the use of any drug that could interfere with measurement or assessment of serum androgen levels is prohibited, including 5 alpha-reductase inhibitors, anabolic steroids, and drugs with antiandrogenic properties (e.g., spironolactone, cimetidine, flutamide, bicalutamide, and ketoconazole). These drugs must be stopped for at least 1 month prior to study entry (6 months in the case of dutasteride).

The use of over-the-counter products including natural health products (e.g., food supplements and herbal supplements such as saw palmetto or phytoestrogens) that may

affect total T levels within 7 days prior to the first dosing and during the course of the study is prohibited.

7.4.10. Treatment Compliance

Subject compliance with the dosing regimen will be assessed at Days 28, 56, 90, 180, and 270 when study drug is dispensed, and at Day 365 (End-of-Treatment visit) or at Early End of Treatment Visit. Subjects will be instructed to bring any unused and used bottles to each visit. Compliance with SOV2012-F1 will be assessed by capsule counts, and AndroGel compliance will be assessed by weighing the returned pumps.

Subjects who are found to be significantly noncompliant (< 80% or > 120% compliant) based on their individual accountability logs will be treated as follows:

- Re-educated/counselled regarding correct dosing regimen.
- Allowed to continue until next scheduled visit.

If noncompliance continues at the next scheduled visit, subject may be discontinued from the study at the investigator's and sponsor's discretion.

More information about drug accountability for the study is provided in Section 12.1.

7.5. ACTH Stimulation with Synthetic ACTH (Cosyntropin)

ACTH stimulation testing will be performed in a subset of 45 subjects (30 randomized to SOV2012-F1 and 15 randomized to Androgel) at Baseline (Visit 3) and End-of-Treatment visit. Synthetic ACTH1-24 (cosyntropin) will be administered intravenously over two minutes, reconstituted in 2-5 ml of saline, at Time 0 and blood for serum cortisol will be obtained before the administration, and at 30 and 60 minutes after cosyntropin administration

7.6. Removal of Subjects from Therapy or Assessments

Subjects may be discontinued from the study for any of the following reasons:

- Subject request
- Use of nonpermitted concurrent therapy
- Noncompliance with the study drug or study schedule
- Lost to follow-up
- Occurrence of AEs not compatible with the continuation of subject participation in the study, in the investigator's opinion, or unacceptable to the subject to continue.
- Exceeding safety re-test parameters for hemoglobin or prostate-specific antigen (PSA) that require withdrawal from study (see Section 9.1.3.1.2, Hematology and PSA).

Subjects who do not comply with the protocol or who withdraw consent will be discontinued. Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the eCRF.

Subjects withdrawing from the study will be encouraged to complete the same final evaluations at an Early Withdrawal Visit as subjects completing the study according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for subjects who completed the study.

Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts must be documented in the subject's file.

The sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning the investigational product/study drug or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

8. TIMING OF STUDY PROCEDURES

Subjects will provide written informed consent form before any study-related procedures are performed. Subjects may sign informed consent prior to Visit 1; this allows for subjects to complete washout before the first screening visit.

The planned study assessments are presented in Section 7.1.3.

8.1. Pre-treatment Screening Visits

8.1.1. Screening Visit 1 (Day -21 to Day -11)

Screening Visit 1 should occur between 7 a.m. and 10 a.m. and not more than 21 days before initial study medication use.

After the subject provides the signed informed consent form, visit procedures include:

- Assess for eligibility against the inclusion and exclusion criteria.
- Collect full medical history and review concomitant medications.
- Record demographic data, such as race, ethnic origin, and date of birth.
- Draw a blood sample to test total serum T level.

After the procedures, subjects will be given a meal diary to record three days of breakfasts and dinners before the next visit.

Subjects will be offered the opportunity to participate in the ACTH stimulation substudy. Informed consent form addendum for the substudy must be signed by Visit 2.

8.1.2. Screening Visit 2 (Day -10 to Day -7)

Visit 2 will take place a minimum of 4 and not more than 11 days after Screening Visit 1. Subjects should arrive at the clinic between 7 a.m. and 10 a.m., having fasted for at least 8 hours. Subjects should remain well hydrated during fasting and drink at least one glass of water (240 mL or 8 oz) prior to visit. At the investigator's discretion, subjects may be re-screened using the Visit 2 procedures, or individual laboratory tests may be repeated.

Subjects will be contacted the previous day to remind them to fast before Visit 2; no food or drink except water for 8 hrs. Visit procedures include:

- Reassess eligibility against the inclusion and exclusion criteria.
- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.
- Record vital signs (BP, heart rate, weight, and temperature). At all visits, BP will be measured using a cuff appropriate to the subject's arm size, in a standardized manner, i.e., after the subject has rested in the sitting position for 5 minutes. The cuff used for each subject should be noted along with its size, and the same cuff used throughout the study for that subject. Blood pressure measurements will be duplicated within 5 minutes. If the difference in sBP and dBP measurements is >10 mm Hg and > 5 mm Hg, respectively, a third BP measurement will be taken and results averaged.
- Perform an ECG.
- Record height.
- Collect samples for biochemistry (includes T sample), endocrinology, hematology (including glycosylated hemoglobin [HbA1c]), urinalysis, lipid panel, and PSA.
    - Note: If the LDL value cannot be calculated due to triglycerides falling outside the valid range for the central lab's calculation for obtaining LDL, the LDL value should be measured directly. This is done from a second sample and requires an additional visit by the subject once the lipid panel results are received.
- Collect samples for hepatitis B surface antigen and hepatitis C antibody, with confirmatory testing, i.e., detectable serum HCV RNA); collect HIV antibody tests.
- Collect urine sample for drug screening (includes cocaine, narcotics, benzodiazepines, tetrahydrocannabinol, barbiturates, and amphetamines).
- Perform a full physical examination that must include administering an I-PSS questionnaire, assessment for the presence of gynecomastia, and digital rectal examination.
- Collect subject meal diary and enter information into ASA24 system in the presence of the subject
- Collect informed consent form addendum for the ACTH stimulation substudy if the subject is a substudy participant.
- Dispense Psychosexual Daily Questionnaire (PDQ). Subjects will be given the PDQ daily diary booklet to complete for seven consecutive days just before the next visit.

8.2. Study Visits

Visits 3, 10, 12, and 13 require subjects to arrive fasted for the purpose of collecting fasted insulin. Subjects who arrive un-fasted should be allowed to continue these visits, provided they have not also dosed. No insulin sample should be collected for un-fasted subjects. All other samples should be collected.

Visits 4, 6 and 8 require SOV2012-F1 subjects to arrive fasted for the 24-hour PK assessments and fasted insulin. Subjects who arrive un-fasted should be rescheduled. Visits 4, 6 and 8 also require AndroGel subjects to arrive fasted, but the visit may continue except that fasted insulin sample is not collected. All other samples are collected.

Throughout the study, subjects should be reminded that if a partner becomes pregnant, subject should inform the clinic.

8.2.1. Visit 3, Day 1 (Baseline)

Visit 3 occurs on Day 1 and will take place within 10 days of Visit 2. All inclusionary/exclusionary lab results must be available, and subjects should have completed the 7-day PDQ Questionnaire. The following procedures for all subjects will be performed at Visit 3. Subjects should arrive at the clinic between 7 a.m. and 10 a.m., having fasted for at least 8 hours. Subjects will be contacted the previous day to remind them to fast before Visit 3; no food or drink except water for 8 hrs. Subjects should remain well hydrated during fasting and drink at least one glass of water (240 mL or 8 oz) prior to visit.

- Reassess for study eligibility against the inclusion and exclusion criteria.
    - Note: If the central lab cannot determine LDL from the initial Visit 2 sample, then direct measurement of LDL from a sample is required to obtain an LDL value for comparison to inclusion criterion 5c. This situation occurs if the triglycerides fall outside of the valid ranges for the calculation approach for determining LDL.
- Remind the subject that if a partner becomes pregnant, subject should inform the clinic.
- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.
- Record vital signs (BP, heart rate, weight, and temperature). At all visits, BP will be measured using a cuff appropriate to the subject's arm size, in a standardized manner, i.e., after the subject has rested in the sitting position for 5 minutes. The cuff used for each subject should be noted along with its size, and the same cuff used throughout the study for that subject. Blood pressure measurements will be duplicated within 5 minutes. If the difference in sBP and dBP measurements is > 10 mm Hg and > 5 mm Hg, respectively, a third BP measurement will be taken and the results averaged.
- Randomize eligible subjects and provide each with a subject number.
- Collect samples for fasting insulin, and estradiol (E2). For subjects assigned to SOV2012-F1, collect blood sample for T and DHT in plasma tube and for

subjects assigned to AndroGel, collect blood sample for T and DHT in serum tube.

- Record symptom-directed physical examination.
- Dispense and collect SF-36, and IIEF. Collect the PDQ that was dispensed at the prior visit.
- Dispense study medications.
- Subjects will be provided with a standardized breakfast after testing and lab sample collection is complete.
- Subjects randomized to SOV2012-F1 will be observed taking their first dose (400 mg) with breakfast provided at the clinic. Subjects should take the dose 30 (±5) minutes after the start of the meal.
- Subjects randomized to AndroGel will be instructed to apply the gel topically in the morning to the shoulders and upper arms, starting at 2 pump actuations (40.5 mg). Priming of the pump will be demonstrated. The first dose administration will be observed in the clinic. A breakfast will be offered.
- SOV2012-F1 subjects will be given meal menus to select breakfast and dinner for future PK visits based on ASA24 output of their eating habits (low fat or normal fat or high fat breakfast and dinner with appropriate Kcals).
- AndroGel subjects will be given the normal fat menu for all selections.
- Subjects participating in the ACTH stimulation substudy will undergo the ACTH stimulation test. Synthetic $ACTH_{1-24}$ (cosyntropin) will be reconstituted in 2-5ml of saline and administered intravenously over 2 minutes at Time 0 and blood for serum cortisol will be obtained before administration, and at 30 and 60 minutes after cosyntropin administration. The test should be performed at the same time on Day 1 and Day 365. On D365, the zero timepoint sample should be submitted for cortisol binding globulin, and the 30min and 60min samples submitted for serum cortisol.

When all the baseline procedures have been performed, the next visit will be scheduled.

8.3. Treatment Period

8.3.1. Visit 4, Day 14(±2)

Visit 4 will take place on Day 14(±2 days). Subjects should arrive at the clinic between 7 and 10 a.m., having fasted for at least 8 hours. Subjects will be contacted the previous day to remind them to:

- Fast before Visit 4; no food or drink except water for 8 hrs. Subjects should remain well hydrated during fasting and drink at least one glass of water (240 mL or 8 oz) prior to visit.
- Bring their study medications.
- Not ingest, or apply, their study medication in the morning before coming to the clinic.

Subjects should have taken any concomitant medications before arriving at the clinic. The following procedures will be performed at Visit 4:

SOV2012-F1 Group (Overnight Stay)

- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.
- Record vital signs including a single BP within 60 minutes prior to dosing, and then a single BP at 4-hour intervals (4, 8, 12, 16, 20, and 24 hours).
- Collect samples to assess biochemistry, fasting insulin, and lipid panel.
- Collect blood samples predose and at 1.5, 3, 4, 5, 6, 8, 12, 13.5, 15, 16, 17, 18, 20, and 24 hours after a.m. dose (±5 minutes for all timepoints) for 24-hour PK analysis of plasma T and DHT. Dinner should begin at 11.5 hours (±10 minutes) after the morning dose, and the 12-hour sample is taken immediately before the evening dose. Subjects should take the morning and evening doses 30 (±5) minutes after the start of breakfast and the evening meal, respectively.
- Record symptom-directed physical examination.
- Provide meals based on subjects' ASA24 records, and record meals, meal fat type, and the percentage of meal consumed (0, 25%, 50%, 75%, 100%).

AndroGel Group (Single-Day Visit)

- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.
- Record vital signs (BP, heart rate, weight, and temperature). At all visits, BP will be measured using a cuff appropriate to the subject's arm size, in a standardized manner, i.e., after the subject has rested in the sitting position for 5 minutes. The cuff used for each subject should be noted along with its size, and the same cuff used throughout the study for that subject. Blood pressure measurements will be duplicated within 5 minutes. If the difference in sBP and dBP measurements is >10 mm Hg and > 5 mm Hg, respectively, a third BP measurement will be taken and results averaged.
- Collect samples to assess biochemistry, fasting insulin, and lipid panel.
- Collect single-draw predose PK blood sample for serum T and DHT.
- Record symptom-directed physical examination.
- Provide breakfast of choice based on normal fat menu selections.

When all procedures have been performed, the next visit will be scheduled.

8.3.2. Visit 5, Day 28(±2)

Visit 5 will take place between 7 a.m. and 10 a.m. on Day 28(±2 days). Subjects will be contacted the previous day to remind them to:

- Take any concomitant medications before arriving at the clinic, with a few sips of water.

- Ingest, or apply, their study medication that morning, before arriving at the clinic.

The following procedures will be performed for all subjects at Visit 5:

- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.
- Record vital signs (BP, heart rate, weight, and temperature). At all visits, BP will be measured using a cuff appropriate to the subject's arm size, in a standardized manner, i.e., after the subject has rested in the sitting position for 5 minutes. The cuff used for each subject should be noted along with its size, and the same cuff used throughout the study for that subject. Blood pressure measurements will be duplicated within 5 minutes. If the difference in sBP and dBP measurements is > 10 mm Hg and > 5 mm Hg, respectively, a third BP measurement will be taken and results averaged.
- Remind the subject that if a partner becomes pregnant, subject should inform the clinic.
- Record symptom-directed physical examination.
- Based on the dose-titration algorithms and the results from Visit 4, adjust dose if needed. The dose regimen will be communicated to the site via the IWRS.
- Inquire if subject missed any doses.
- Dispense drug based on dose for the next study interval, including any dose adjustment.
    - SOV2012-F1–treated subjects will begin their new dose regimen with the evening dose.
    - AndroGel-treated subjects will begin their new dose regimen with the next day's dose.

When all of the above and accountability check procedures have been performed, the next visit will be scheduled.

8.3.3. Visit 6, Day 42(±2)

Visit 6 will take place on Day 42(±2 days). Subjects should arrive at the clinic between 7 and 10 a.m., having fasted for at least 8 hours. Subjects will be contacted the previous day to remind them to:

- Fast before Visit 6; no food or drink except water for 8 hrs. Subjects should remain well hydrated during fasting and drink at least one glass of water (240 mL or 8 oz) prior to visit.
- Bring their study medications.
- Not ingest, or apply, their study medication in the morning before coming to the clinic.

Subjects should have taken any concomitant medications before arriving at the clinic. The following procedures will be performed at Visit 6:

SOV2012-F1 Group (Overnight Stay)

- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.
- Record vital signs including a single BP within 60 minutes prior to dosing, and then a single BP at 4-hour intervals (4, 8, 12, 16, 20, and 24 hours).
- Collect samples to assess biochemistry, fasting insulin, and lipid panel.
- Collect blood samples pre-dose and at 1.5, 3, 4, 5, 6, 8, 12, 13.5, 15, 16, 17, 18, 20, and 24 hours after a.m. dose (±5 minutes for all timepoints) for 24-hour PK analysis of plasma T and DHT. Dinner should begin at 11.5 hours ((±10 minutes) after the morning dose, and the 12-hour sample is taken immediately before the evening dose. Subjects should take the morning and evening doses 30 (±5) minutes after the start of breakfast and the evening meal, respectively.
- Record symptom-directed physical examination.
- Provide meals based on subjects' ASA24 records, and record meals, meal fat type, and the percentage of meal consumed (0, 25%, 50%, 75%, 100%) for breakfast and dinner.

AndroGel Group (Single-Day Visit)

- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.
- Record vital signs (BP, heart rate, weight, and temperature). At all visits, BP will be measured using a cuff appropriate to the subject's arm size, in a standardized manner, i.e., after the subject has rested in the sitting position for 5 minutes. The cuff used for each subject should be noted along with its size, and the same cuff used throughout the study for that subject. Blood pressure measurements will be duplicated within 5 minutes. If the difference in sBP and dBP measurements is > 10 mm Hg and > 5 mm Hg, respectively, a third BP measurement will be taken and results averaged.
- Record symptom-directed physical examination.
- Collect samples to assess biochemistry, fasting insulin, and lipid panel.
- Collect single-draw PK predose blood sample for serum T and DHT.
- Provide breakfast of choice based on normal fat menu selections. When all procedures have been performed, the next visit will be scheduled.

8.3.4. Visit 7, Day 56(±2)

Visit 7 will take place between 7 a.m. and 10 a.m. on Day 56(±2 days). Subjects will be contacted the previous day to remind them to:

- Take any concomitant medications before arriving at the clinic.
- Ingest, or apply, their study medication (30 (±5) minutes after start of meal for SOV2012-F1–treated subjects) that morning, before arriving at the clinic.

- Bring their study medication to the clinic.

The following procedures will be performed for all subjects at Visit 7:

- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.
- Record vital signs (BP, heart rate, weight, and temperature). At all visits, BP will be measured using a cuff appropriate to the subject's arm size, in a standardized manner, i.e., after the subject has rested in the sitting position for 5 minutes. The cuff used for each subject should be noted along with its size, and the same cuff used throughout the study for that subject. Blood pressure measurements will be duplicated within 5 minutes. If the difference in sBP and dBP measurements is > 10 mm Hg and > 5 mm Hg, respectively, a third BP measurement will be taken and results averaged.
- Record symptom-directed physical examination.
- Based on the dose titration algorithms and the results from Visit 6, adjust dose if needed. The dose regimen will be communicated to the site via the IWRS.
- Inquire if subject missed any doses.
- Dispense drug based on dose for the next study interval, including any dose adjustment. (SOV2012-F1–treated subjects will begin their new dose regimen with the evening dose. AndroGel-treated subjects will begin their new dose regimen with the next day's dose.)
- Dispense Psychosexual Daily Questionnaire (PDQ). Subjects will be given a daily diary booklet to complete for seven consecutive days just before the next visit.

When all of the above and accountability check procedures have been performed, the next visit is scheduled.

8.3.5. Visit 8, Day 90(±3)

Visit 8 will take place on Day 90(±3 days). Subjects should arrive at the clinic between 7 and 10 a.m., having fasted for at least 8 hours. Subjects will be contacted the previous day to remind them to:

- Fast before Visit 8; no food or drink except water for 8 hrs. Subjects should remain well hydrated during fasting and drink at least one glass of water (240 mL or 8 oz) prior to visit.
- Bring their study medications with them.
- Not ingest, or apply, their study medication in the morning before coming to the clinic.
- Bring completed PDQ

Subjects should have taken any concomitant medications before arriving at the clinic. The following procedures will be performed at Visit 8:

SOV2012-F1 Group (Overnight Stay)

- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.
- Record vital signs including a single BP within 60 minutes prior to dosing, and then a single BP at 4-hour intervals (4, 8, 12, 16, 20, and 24 hours).
- Collect samples to assess biochemistry, endocrinology, hematology, fasting insulin, PSA, and lipid panel.
- Collect blood samples pre-dose and at 1.5, 3, 4, 5, 6, 8, 12, 13.5, 15, 16, 17, 18, 20, and 24 hours after a.m. dose (±5 minutes for all timepoints) for 24-hour PK analysis of plasma T and DHT; plasma TU and DHTU; and E2. Dinner should begin at 11.5 hours (±10 minutes) after the morning dose, and the 12-hour sample is taken immediately before the evening dose. Subjects should take the morning and evening doses 30 (±5) minutes after the start of breakfast and the evening meal, respectively.
- Perform a full physical examination that must include administering an I-PSS questionnaire, assessment for the presence of gynecomastia, and digital rectal examination.
- Inquire if subject missed any doses.
- Dispense and collect SF-36, and IIEF. Collect the PDQ that was dispensed at the prior visit.
- Provide meals based on subjects' ASA24 records, and record meals, meal fat type, and the percentage of meal consumed (0, 25%, 50%, 75%, 100%) for breakfast and dinner.
- Dispense drug based on dose for the next study

interval. AndroGel Group (Overnight Stay)

- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.
- Record vital signs including a single BP within 60 minutes prior to dosing, and then a single BP at 4-hour intervals (4, 8, 12, 16, 20, and 24 hours).
- Collect samples to assess biochemistry, endocrinology, hematology, fasting insulin, PSA, and lipid panel.
- Collect pre-dose blood samples and at 2, 4, 8, 12, 16, 20, and 24 hours post dose for 24-hour PK analysis of T and DHT in serum, and E2 in plasma for AndroGel-treated subjects.
- Perform a full physical examination that must include administering an I-PSS questionnaire, assessment for the presence of gynecomastia, and digital rectal examination.
- Dispense and collect SF-36, and IIEF. Collect the PDQ that was dispensed at the prior visit.

- Provide breakfast of choice based on normal fat menu selections. Inquire if subject missed any doses.
- Dispense drug based on dose for the next study interval.

When all of the above and accountability check procedures have been performed, the next visit will be scheduled.

If analysis of the Day 90 24-hour PK data reveals that a subject is on an incorrect dose, discontinuation of the subject may be appropriate, as detailed in Section 7.1. If a SOV2012- F1–treated subject has T Cavg below the normal range (2.5% percentile) on Day 90 the subject may be dose-titrated at an unscheduled visit, if the efficacy period data suggests benefit to the subject and an acceptable safety profile.

8.3.6. Visit 9, Day 166(±3)

Visit 9 will take place on Day 166(±3 days). Subjects will be contacted the previous day to remind them to:

- Take any concomitant medications before arriving at the clinic.
- For AndroGel-treated subjects, arrive at the clinic from 7 a.m. to 10 a.m. and not apply their morning dose before arriving.
- For SOV2012-F1–treated subjects, eat a normal breakfast and take their morning dose 30 (±5) minutes after beginning that meal. They are then to arrive at the clinic in time for a single blood draw after taking their morning dose within 3 to 5 hours. Subjects should record the time of the morning dose.

The following procedures will be performed at Visit 9:

SOV2012-F1 Group

- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.
- Record vital signs (BP, heart rate, weight, and temperature). At all visits, BP will be measured using a cuff appropriate to the subject's arm size, in a standardized manner, i.e., after the subject has rested in the sitting position for 5 minutes. The cuff used for each subject should be noted along with its size, and the same cuff used throughout the study for that subject. Blood pressure measurements will be duplicated within 5 minutes. If the difference in sBP and dBP measurements is > 10 mm Hg and > 5 mm Hg, respectively, a third BP measurement will be taken and results averaged.
- Obtain a single PK blood sample for plasma T and DHT within 3 to 5 hours after the morning dose
- Record symptom-directed physical examination.
- Dispense and collect IIEF. Dispense PDQ. Subjects will be given the PDQ daily diary booklet to complete for seven consecutive days just before the next visit.

AndroGel Group

- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.
- Record vital signs (BP, heart rate, weight, and temperature). At all visits, BP will be measured using a cuff appropriate to the subject's arm size, in a standardized manner, i.e., after the subject has rested in the sitting position for 5 minutes. The cuff used for each subject should be noted along with its size, and the same cuff used throughout the study for that subject. Blood pressure measurements will be duplicated within 5 minutes. If the difference in sBP and dBP measurements is >10 mm Hg and > 5 mm Hg, respectively, a third BP measurement will be taken and results averaged.
- Collect single predose PK blood sample for AndroGel for serum T and DHT.
- Record symptom-directed physical examination.
- Dispense and collect IIEF. Dispense PDQ. Subjects will be given the PDQ daily diary booklet to complete for seven consecutive days just before the next visit.
- Subject may choose to apply the AndroGel dose at the clinic.

When all procedures have been performed, the next visit will be scheduled.

8.3.7. Visit 10, Day 180(±3)

Visit 10 will take place between 7 a.m. and 10 a.m. on Day 180(±3 days). Subjects will be contacted previous day to remind them to:

- Take any concomitant medications before arriving at the clinic.
- Fast for 8 hours before arriving at the clinic; no food or drink except water. Subjects should remain well hydrated during fasting and drink at least one glass of water (240 mL or 8 oz) prior to visit.
- Bring their study medication to the clinic.
- Bring completed PDQ

The following procedures will be performed for all subjects at Visit 10:

- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.
- Record vital signs (BP, heart rate, weight, and temperature). At all visits, BP will be measured using a cuff appropriate to the subject's arm size, in a standardized manner, i.e., after the subject has rested in the sitting position for 5 minutes. The cuff used for each subject should be noted along with its size, and the same cuff used throughout the study for that subject. Blood pressure measurements will be duplicated within 5 minutes. If the difference in sBP and dBP measurements is >10 mm Hg and > 5 mm Hg, respectively, a third BP measurement will be taken and results averaged.

- Collect samples to assess biochemistry, hematology, fasting insulin, PSA, and lipid panel.
- Record symptom-directed physical examination.
- Based on the dose titration algorithms and the results from Visit 9, adjust dose if needed. The dose regimen will be communicated to the site via the IWRS.
- Inquire if subject missed any doses.
- Dispense drug based on dose for the next study interval, including any dose adjustment.
- Retain the study medication container (bottle or pump) from Visit 8.
- Collect PDQ dispensed at the prior visit.
- Provide breakfast to all subjects.
    - SOV2012-F1–treated subjects should take their morning dose with breakfast based on the ASA24 data for the subject, 30 (±5) minutes after beginning the meal.
    - **Bioanalytical Sample Stability Substudy Only:** SOV2012-F1 subjects enrolled in the Bioanalytical Sample Stability Substudy should receive a high-fat breakfast of at least 700 kcal (regardless of ASA24 data) and take their morning dose 30 (±5) minutes after beginning the meal.
    - AndroGel subjects may be given any normal fat breakfast of their choice.
- AndroGel-treated subjects may choose to apply their morning dose at the clinic.
- **Bioanalytical Sample Stability Substudy Only:** Subjects may participate on either V10 (Day 180) or V12 (Day 270), or at an unscheduled visit within a week of either but will not participate at both visit timepoints. Samples will be collected beginning 3 to 3.5 hours after subjects take the morning dose 30 (±5) minutes after beginning the high-fat breakfast. Samples will be collected over approximately a 30-45-minute period, and according to details provided in the Laboratory Manual.

When all the above and accountability check procedures have been performed, the next visit is scheduled.

8.3.8. Visit 11, Day 256(±3)

Visit 11 will take place on Day 256(±3 days). Subjects will be contacted the previous day to remind them to:

- Take any concomitant medications before arriving at the clinic.
- For AndroGel-treated subjects, to arrive at the clinic from 7 a.m. to 10 a.m. and not apply their morning dose before arriving.
- For SOV2012-F1–treated subjects, to eat a normal breakfast and to take their morning dose 30 (±5) minutes after beginning that meal. They are then to arrive at

the clinic for a single blood draw within 3 to 5 hours after taking their morning dose. Subjects should record the time of the morning dose.

The following procedures will be performed at Visit 11:

SOV2012-F1 Group

- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.
- Record vital signs (BP, heart rate, weight, and temperature). At all visits, BP will be measured using a cuff appropriate to the subject's arm size, in a standardized manner, i.e., after the subject has rested in the sitting position for 5 minutes. The cuff used for each subject should be noted along with its size, and the same cuff used throughout the study for that subject. Blood pressure measurements will be duplicated within 5 minutes. If the difference in sBP and dBP measurements is > 10 mm Hg and > 5 mm Hg, respectively, a third BP measurement will be taken and results averaged.
- Obtain a single PK blood sample for plasma T and DHT within 3 to 5 hours after the morning dose.
- Record symptom-directed physical examination.
- Dispense and collect IIEF. Dispense Psychosexual Daily Questionnaire (PDQ). Subjects will be given a daily diary booklet to complete for seven consecutive days just before the next visit.

AndroGel Group

- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.
- Record vital signs (BP, heart rate, weight, and temperature). At all visits, BP will be measured using a cuff appropriate to the subject's arm size, in a standardized manner, i.e., after the subject has rested in the sitting position for 5 minutes. The cuff used for each subject should be noted along with its size, and the same cuff used throughout the study for that subject. Blood pressure measurements will be duplicated within 5 minutes. If the difference in sBP and dBP measurements is >10 mm Hg and > 5 mm Hg, respectively, a third BP measurement will be taken and results averaged.
- Collect single-draw predose PK blood sample for serum T and DHT.
- Record symptom-directed physical examination.
- Dispense and collect IIEF. Dispense Psychosexual Daily Questionnaire (PDQ). Subjects will be given a daily diary booklet to complete for seven consecutive days just before the next visit.
- Subject may choose to apply the AndroGel dose at the clinic.

When all of these procedures have been performed, the next visit will be scheduled.

8.3.9. Visit 12, Day 270(±3)

Visit 12 will take place between 7 a.m. and 10 a.m. on Day 270(±3 days). Subjects should be contacted the previous day to remind them to:

- Take any concomitant medications before arriving at the clinic.
- Fast for 8 hours before arriving at the clinic; no food or drink except water. Subjects should remain well hydrated during fasting and drink at least one glass of water (240 mL or 8 oz) prior to visit.
- Bring their study medication to the clinic.
- Bring completed PDQ

The following procedures will be performed for all subjects at Visit 12:

- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.
- Record vital signs (BP, heart rate, weight, and temperature). At all visits, BP will be measured using a cuff appropriate to the subject's arm size, in a standardized manner, i.e., after the subject has rested in the sitting position for 5 minutes. The cuff used for each subject should be noted along with its size, and the same cuff used throughout the study for that subject. Blood pressure measurements will be duplicated within 5 minutes. If the difference in sBP and dBP measurements is > 10 mm Hg and > 5 mm Hg, respectively, a third BP measurement will be taken and results averaged.
- Collect samples to assess biochemistry, hematology, fasting insulin, PSA, and lipid panel.
- Record symptom-directed physical examination.
- Based on the dose-titration algorithms and the results from Visit 11, adjust dose if needed. The dose regimen will be communicated to the site via the IWRS.
- Inquire if subject missed any doses.
- Dispense drug based on dose for the next study interval, including any dose adjustment.
- Retain the study medication container (bottle or pump) from Visit 10.
- Collect PDQ dispensed at the prior visit.
- Dispense PDQ. Subjects will be given the PDQ daily diary booklet to complete for seven consecutive days just before the next visit.
- Provide breakfast to all subjects.
    - SOV2012-F1–treated subjects should take their morning dose with breakfast based on the ASA24 data for the subject, 30 (±5) minutes after beginning the meal.
    - **Bioanalytical Sample Stability Substudy Only:** SOV2012-F1 subjects enrolled in the Bioanalytical Sample Stability Substudy should receive a

high-fat breakfast of at least 700 kcal (regardless of ASA24 data) and take their morning dose 30 (±5) minutes after beginning the meal.

- AndroGel subjects may be given any normal fat breakfast of their choice.

- AndroGel-treated subjects may choose to apply their morning dose at the clinic.
- **Bioanalytical Sample Stability Substudy Only:** Subjects may participate on either V10 (Day 180) or V12 (Day 270), or at an unscheduled visit within a week of either but will not participate at both visit timepoints. Samples will be collected beginning 3 to 3.5 hours after subjects take the morning dose 30 (±5) minutes after beginning the high-fat breakfast. Samples will be collected over approximately a
30-45-minute period, and according to details provided in the Laboratory Manual.

MRS-TU-2019EXT Substudy- Please refer to Appendix 16.12 for Schedule of Assessments which begins at Day 364 for subjects participating in the MRS-TU-2019EXT ABPM Extension study.

8.3.10. End of Treatment, Day 365(±3)

End of Treatment visit will take place for all subjects, including early withdrawal subjects and those completing the treatment period. For subjects completing the treatment period, End of Treatment visit takes place on Day 365(±3). Subjects should arrive at the clinic between 7 a.m. and 10 a.m., having fasted for at least 8 hours. The previous day, all subjects will be contacted to remind them to:

- **Subjects should arrive in a fasted** state for End of Treatment visit; no food or drink for at least 8 hours, **except** water (does not apply to early withdrawal subjects). Subjects should remain well hydrated during fasting and drink at least one glass of water (240 mL or 8 oz) prior to visit.
- **Subject should not smoke within 30min of the start of the visit**, because in- clinic BP and Heart Rate are being assessed.
- Bring their study medication to the clinic.
- Bring completed PDQ
- Not ingest, or apply, their study medication in the morning before coming to the clinic.
- Take any concomitant medications before arriving at the clinic.

The following procedures will be performed at End of Treatment visit: <u>For all</u> <u>subjects</u>

- *Subjects participating in MRS-TU-2019EXT ABPM Extension Study, must have ABPM downloads completed (pass or fail), prior to other visit assessments. Please refer to Appendix 16.12 for details.
- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.

- Record vital signs (BP, heart rate, weight, and temperature). At all visits, BP will be measured using a cuff appropriate to the subject's arm size, in a standardized manner, i.e., after the subject has rested in the sitting position for 5 minutes. The cuff used for each subject should be noted along with its size, and the same cuff used throughout the study for that subject. Blood pressure measurements will be duplicated within 5 minutes. If the difference in sBP and dBP measurements is > 10 mm Hg and > 5 mm Hg, respectively, a third BP measurement will be taken and results averaged.
- Collect samples to assess biochemistry, endocrinology, hematology (to include glycosylated hemoglobin or HbA1c), fasting insulin, PSA, and lipid panel (fasting insulin does not apply for early withdrawal subjects).
- Perform a full physical examination that must include administering an I-PSS questionnaire, assessment for the presence of gynecomastia, and digital rectal examination.
- Dispense and collect SF-36, and IIEF. Collect PDQ dispensed at the prior visit.
- Drug containers (bottles and pumps) from the completed dosing period will be retained for accountability.
- For subjects participating in the ACTH stimulation substudy, synthetic $ACTH_{1-24}$ (cosyntropin) will be administered intravenously over 2 minutes

  reconstituted in 2-5 mL of saline at Time 0 and blood for serum cortisol will be obtained before and 30 and 60 minutes after cosyntropin administration. This does not apply to early withdrawal subjects. The ACTH test should be performed at the same time of the day as performed on Day 1.
- Ask subjects if a partner has become pregnant at any time during the study.

SOV2012-F1 Group (does not apply to early withdrawal subjects)

- Provide breakfast to SOV2012-F1–treated subjects, who should take their morning dose 30 (±5) minutes after beginning breakfast. Subjects to record the time of dose.
- Subjects should be present at the clinic within 3-5 hours (±10 min) after the morning dose for a single blood draw to measure plasma T and DHT.

AndroGel Group (does not apply to early withdrawal subjects)

- Collect single-draw predose PK blood sample for serum T and DHT, prior to full physical examination.
- Offer breakfast.

***MRS-TU-2019EXT Substudy:** Please refer to Appendix 16.12 for **Schedule of Assessments** which begins at Day 364 for subjects continuing fromMRS-TU-2019 main study. A modified schedule of assessments is also available in 16.12.1- 16.12.2 for subjects having completed MRS-TU-2019 main study, prior to the start of MRS-TU-2019EXT, and for new enrollment subjects (naïve to MRS-TU-2019) wishing to enroll in MRS-TU-2019EXT.*

8.3.11. Follow-Up Visit, Day 14(±3) After Last Dose of Study Medication in MRS-TU-2019

The Follow up Visit will take place 14(±3) days after the last dose of study medication. The following procedures will be performed for all subjects by telephone at the Follow up Visit:

- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.

8.4. Duration of Treatment in MRS-TU-2019

The duration of treatment will be approximately 365 days, plus up to 21 days for screening and 14(±3) days for the Follow up Visit.

9. EFFICACY, PHARMACOKINETICS, AND SAFETY VARIABLES

The planned Schedule of Assessments is in Section 7.1.3.

9.1. Efficacy, Pharmacokinetics, and Safety Measurements Assessed

9.1.1. Efficacy Variables

9.1.1.1. Average Plasma Total Testosterone

The primary efficacy variable in this study of SOV2012-F1 is plasma T C_{avg} as measured by mass spectrometry. Efficacy will be determined by the percentage of subjects with male hypogonadism with T C_{avg} within the normal range after 90 days of treatment.

At Day 14, Day 42, and Day 90, 24-hour serial blood samples will be collected for all subjects predose and 1.5, 3, 4, 5, 6, 8, 12, 13.5, 15, 16, 17, 18, 20, and 24 hours after a.m. dosing (±5 minutes for each timepoint).

These samples will be used to determine the total T C_{avg} values critical for assessing the primary endpoint.

9.1.1.2. Maximum Plasma Testosterone Concentration

The secondary efficacy variable in this study is plasma T C_{max} as measured by mass spectrometry. Efficacy will be determined by the percentage of SOV2012-F1–treated subjects with T C_{max} values (a) < 1500 ng/dL; (b) 1800 to 2500 ng/dL, and (c) > 2500 ng/dL after 90 days of treatment.

At Day 14, Day 42, and Day 90, 24-hour serial blood samples will be collected for all subjects pre-dose and 1.5, 3, 4, 5, 6, 8, 12, 13.5, 15, 16, 17, 18, 20, and 24 hours after a.m. dose (±5 minutes for each timepoint).

These samples will be used to determine the total T C_{max} values critical for assessing the secondary endpoint.

9.1.2. Pharmacokinetic Variables

9.1.2.1. SOV2012-F1 group

For the SOV2012-F1 group, a blood sample (plasma) for determination of T, DHT, and E2 will be collected pre-morning dose at Day 1. In addition, 24-hour, intensive blood samples (plasma) will be collected at Day 14; Day 42; and Day 90 for all subjects pre-dose and 1.5, 3, 4, 5, 6, 8, 12, 13.5, 15, 16, 17, 18, 20, and 24 hours after a.m. dose (±5 minutes for each timepoint) for T and DHT. Blood samples (plasma) for TU, DHTU, and E2 determination will be also collected on Day 90 for all subjects pre-dose and 1.5, 3, 4, 5, 6, 8, 12,13.5, 15, 16, 17, 18, 20, and 24 hours after a.m. dosing (±5 minutes for each timepoint). A single blood draw PK sample (plasma) for measuring T and DHT will be collected for all subjects 3 to 5 hours after a.m. dose at Day 166, Day 256, and Day 365.

The concentrations of calculated free testosterone (free T) will be calculated using the FTZ method [28,29].

The time of dosing and each blood sampling will be recorded to the minute according to nominal scheduled timepoints listed in Table 9-1.

Table 9-1 Scheduled Nominal Timepoints for SOV2012-F1 Pharmacokinetic Blood Samples

Study Visit / Day	Analytes	Blood Samples Assay Time Points
Visit 3 / Day 1	T, DHT, E2	Pre-morning dose
Visit 4 / Day 14	T, DHT	Pre-morning dose and 1.5, 3, 4, 5, 6, 8, 12, 13.5, 15, 16, 17, 18, 20, and 24 hours after a m. dose
Visit 6 / Day 42	T, DHT	Pre-morning dose; 1.5, 3, 4, 5, 6, 8, 12, 13.5, 15, 16, 17, 18, 20, and 24 hours after a m. dose
Visit 8 / Day 9a[m]	TU, DHTU, T, DHT, E2	Pre-morning dose; 1.5, 3, 4, 5, 6, 8, 12, 13.5, 15, 16, 17, 18, 20 and 24 hours after a m. dose
Visit 9/ Day 166	T, DHT	3-5 hours after a m. dose
Visit 11/ Day 256	T, DHT	3-5 hours after a m. dose
Visit 13/ Day 365	T, DHT	3-5 hours after a m. dose

9.1.2.2. AndroGel group

For the AndroGel group, a pre-morning dose blood sample for determination of T and DHT (serum), and E2 (plasma) will be collected at Day 1. In addition, 24-hour, intensive blood samples will be collected at Day 90 for determination of T and DHT in serum, and E2 in plasma in all subjects pre-morning dose and 2, 4, 8, 12, 16, 20 and 24 hours after dosing (±5 minutes for each timepoint). Furthermore, a pre-morning dose blood sample for determination of T and DHT (serum) will be collected at Day 14, Day 42, Day 166, Day 256, and Day 365.

The time of dosing and each blood sampling will be recorded to the minute according to nominal scheduled timepoints listed in Table 9-2

Table 9-2 Scheduled Nominal Timepoints for AndroGel Pharmacokinetic Blood Samples

Study Visit / Day	Analytes	Blood Samples Assay Time Points
Visit 3 / Day 1	T, DHT, E2	Pre-morning dose
Visit 4 / Day 14	T, DHT	Pre-morning dose
Visit 6 / Day 42	T, DHT	Pre-morning dose
Visit 8 / Day 90	T, DHT, E2	Pre-morning dose; 2, 4, 8, 12, 16, 20 and 24 hours
Visit 9/ Day 166	T, DHT	Pre-morning dose
Visit 11/ Day 256	T, DHT	Pre-morning dose
Visit 13/ Day 365	T, DHT	Pre-morning dose

Abbreviations: DHT = dihydrotestosterone; E2 = estradiol; T = testosterone.

9.1.3. Safety Assessments

9.1.3.1. Adverse Events Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product 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 it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study, beginning once the Informed Consent is signed. AEs will be elicited by asking the subject a non-leading question, for example, “Have you experienced any new or changed symptoms since we last asked/since your last visit?” AEs should be recorded on the appropriate page of the eCRF.

Assessment of Severity

Each AE will be assigned a category by the investigator as follows:

Mild: An AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.

Moderate: An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.

Severe: An AE that prevents normal everyday activities; treatment or other intervention usually needed.

If there is a change in severity of an AE, it must be recorded as a separate event.

Assessment of Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drug. Causality should be assessed using the categories presented in the following table:

Unrelated:	Clinical event with an incompatible time relationship to study drug administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the study drug.
Possible:	Clinical event with a reasonable time relationship to study drug administration, but that could also be explained by concurrent disease or other drugs or chemicals.
Probable:	Clinical event with a reasonable time relationship to study drug administration and is unlikely to be attributed to concurrent disease or other drugs or chemicals.

Action Taken

The investigator will describe the action taken in the appropriate section of the eCRF, as follows:

- None
- Study drug stopped
- Study drug temporarily interrupted
- Concomitant medication
- Other, specify

Follow-up of Adverse Events

All investigators should follow up subjects with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic.

Details of AE resolution must be documented in the eCRF.

Subjects should be followed up for 14 days after receiving the last dose of study drug, and any AEs that occur during this time should be recorded according to the procedures outlined above.

Documentation and Reporting of Adverse Events

Adverse events should be recorded / documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant eCRF pages. The following data should be documented for each AE:

- Description of the symptom event
- Classification of ‘serious’ or ‘not serious’
- Severity

- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship, if any, with study drug
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

9.1.3.1.1. Serious Adverse Events SAE Definition

An SAE is any untoward medical occurrence or effect that, at any dose,

- Results in death.
- Is life-threatening (an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, i.e., it does not include a reaction that might have caused death if it had occurred in a more serious form).
- Requires or prolongs inpatient hospitalization. Complications occurring during hospitalization are AEs and SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing

  non-worsening condition is not, however, considered an AE. The details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF.
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions).
- Results in a congenital anomaly/birth defect.

In addition, medical and scientific judgment is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent 1 of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational product.

Reporting of Serious Adverse Events

Any SAE must be recorded by the investigator if it occurs during the clinical study or within 14 days of receiving the study drug, whether or not the SAE is considered to be related to the investigational product. An SAE report consists of the SAE form, the AE form, and the concomitant medication form. A copy of these forms must be faxed **within 24 hours** for the attention of the product safety scientist at:

INC Research, LLC a Syneos Health Company, Safety and Pharmacovigilance Fax number: +[redacted]

Email: [redacted]

The investigator should not wait to receive additional information to fully document the event before notification of an SAE, though additional information may be requested.

Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of study drug administration and linked by the investigator to this study, should be reported to the study monitor.

The sponsor and/or INC Research, LLC a Syneos Health Company will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of subjects, impact on the conduct of the study or alter the institutional review board (IRB) approval/favorable opinion of the study. In addition, INC Research, LLC a Syneos Health Company, on behalf of Marius Pharmaceuticals, will expedite the reporting to all concerned investigators, to the IRB, where required, and to the regulatory authorities of all adverse reactions that are both serious and unexpected.

Unexpected Adverse Reactions Unexpected Adverse Reaction Definition

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the study drug at any dose that is not consistent with the applicable product information (e.g., investigators brochure for an unauthorized investigational medicinal product or summary of product characteristics for an authorized product).

All suspected unexpected serious adverse reactions (SUSARs) will be the subject of expedited reporting. The sponsor and/or INC Research, LLC a Syneos Health Company, shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IRB within 7 days after knowledge by the sponsor of such a case and that relevant follow-up information is communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and IRB within 15 days after knowledge by the sponsor of such a case. All investigators should follow up SUSARs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Post-study SUSARs that occur after the subject has completed the clinical study must be reported by the investigator to the sponsor.

Warnings and Precautions

Virilization has been reported in children who were secondarily exposed to testosterone gel. AndroGel subjects will be cautioned that children should avoid contact with unwashed or unclothed application sites. They will be instructed that men should apply AndroGel to clean, dry, intact skin of the shoulders and upper arms, and not apply it to any other parts of the body including the abdomen, genitals, chest, armpits (axillae), or knees. Healthcare providers should advise patients to strictly adhere to recommended instructions for use (Sections 2.2, 5.2, and 17 of product information [1], Section 16.4).

Per product information, exposure of women or children to AndroGel should be avoided. Contraindications for AndroGel include any use by pregnant or breast-feeding women, as testosterone may cause fetal harm.

Partner Pregnancy Tracking:

Due to the fetal risk described in the AndroGel label, subjects will be reminded that partner's pregnancy should be avoided throughout the duration of study participation. Subjects (both SOV2012-F1 and AndroGel) will be instructed that if a partner pregnancy occurs, it should be reported to the clinical study site and principal investigator. The principal investigator must notify INC's Pharmacovigilance Hotline at 8[redacted] or Email at [redacted] within 24 hours of learning about the pregnancy and must complete the Pregnancy Reporting Form.

Following the notification of a partner pregnancy, Marius Pharmaceuticals will follow the pregnancy through delivery or termination of the pregnancy by way of a Partner Pregnancy Consent.

9.1.3.1.2. Clinical Laboratory Evaluation

A central laboratory will perform all clinical laboratory analyses. Reference ranges will be supplied by the central laboratory and used by the investigator to assess the laboratory data for clinical significance and pathological changes. **Safety retesting parameters are provided for hemoglobin (see Hematology) and prostate-specific antigen (see PSA).**

The total amount of blood to be drawn per study day is provided in Section 16.9 and Section 16.10.

The following laboratory safety tests will be performed at various points throughout the study, as detailed in the Schedule of Assessments (Table 7-1):

Hematology

Hemoglobin (HGB), WBC, and platelets.

For any on-study hemoglobin level that is >18 g/dL, retest the hemoglobin within 2 weeks of the original test. If the repeated hemoglobin is still >18 g/dL, follow the below guidelines
for safety management:

For a subject currently taking SOV2012-F1 at the following total daily doses:

- 200 mg daily dose of SOV: withdraw the patient from the study.
- 400 mg daily dose of SOV: reduce the daily dose to 200 mg/day
- 600 mg daily dose of SOV: reduce the daily dose to 400 mg/day
- 800 mg daily dose of SOV: reduce the daily dose to

  400 mg/day For a subject currently taking Androgel at the

  following doses:
- 1 pump daily dose (20.25 mg) of Androgel: withdraw the patient from the study
- > 1 pump daily dose of Androgel: reduce by 1 pump/day (For ex., reduce 2 pumps daily to 1, reduce 3 pumps daily to 2)

Repeat HGB after Dose Reductions: For any subject who has been dose reduced due to HGB >18 g/dL, repeat HGB within 30 days (± 7) from time of the dose reduction. If the HGB has not fallen below 18 g/dL, the dose should be further reduced, and the HGB again tested after 30(±7) days.

Biochemistry

AST, ALT, total bilirubin, and alkaline phosphatase, creatinine, blood urea nitrogen, estimated glomerular filtration rate (eGFR), lactate dehydrogenase, glucose, total protein, albumin, sodium, potassium, calcium, and phosphorous

Lipid Panel

Total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins, and triglycerides. At Visit 2, LDL is normally calculated from total cholesterol, HDL and triglycerides. If triglyceride levels fall outside the range for valid use of the LDL calculation employed by the central lab, then LDL levels are obtained by a direct measurement on a second sample.

Endocrinology

Luteinizing hormone (LH), follicle-stimulating hormone (FSH), sex hormone–binding globulin (SHBG), and thyroid-stimulating hormone (TSH)

Urinalysis

pH, glucose, ketones, blood, protein, microscopy, and specific gravity

Prostate-specific antigen (PSA)

For any on-study increase in PSA ≥ 0.8 ng/mL from the Visit 2 baseline value, retest the PSA within 2 weeks of the original test.

If the increase for the repeat PSA test is ≥ 0.8 ng/mL over the Visit 2 baseline value, consult the subject's primary care physician and/or urologist regarding historical PSA values and history of prostate health, in order to determine whether the patient can safely continue in the study. If a patient is withdrawn, he should be scheduled for adequate follow-up by his primary physician.

9.1.3.1.3. Other Laboratory Variables

Urine drug screen (testing for cocaine, narcotics, benzodiazepines, tetrahydrocannabinol, barbiturates, and amphetamines) will be performed at Screening Visit 2 only.

Screening for hepatitis B virus surface antigen, HCV antibody, and HIV antibody will be performed at Screening Visit 2 only.

9.1.3.1.4. Vital Signs

Vital signs including BP, heart rate, weight, and temperature will be assessed at each study visit. At all visits, BP will be measured using a cuff appropriate to the subject's arm size, in a standardized manner, i.e., after the subject has rested in the sitting position for 5 minutes. The cuff used for each subject should be noted along with its size, and the same cuff used throughout the study for that subject. Blood pressure measurements on all study visit days will be duplicated

within 5 minutes. If the difference in sBP and dBP measurements is > 10 mm Hg and > 5 mm Hg, respectively, a third BP measurement will be taken and results averaged.

9.1.3.1.5. Physical Examination

Full physical examinations at Screening Visit 2, Visit 8, and End of Treatment must include administration of the I-PSS questionnaire, assessment for the presence of gynecomastia, and digital rectal examination. At all other visits, subjects will undergo a symptom-directed physical examination, focusing on those parts of the physical examination relating to any adverse symptoms the patient may be experiencing, or has experienced during the interval since the last visit.

The I-PSS, a validated questionnaire used to assess the severity and impact of urinary symptoms, will be used to exclude subjects with severe lower urinary tract symptoms.

9.1.3.1.6. Other Safety Assessments

An ECG will be performed at Screening Visit 2 only. Either the PI or a qualified physician (preferably a cardiologist) at the study site (local reader) will interpret all ECGs at that site. The PI or local physician will write on the ECG tracing his/her global interpretation as either "normal ECG," "abnormal ECG - not clinically significant" or "abnormal ECG - clinically significant," then sign and date the ECG. Only the local reader's interpretation of the ECG will be collected. If the local reader is not the principal investigator, the principal investigator will counter-sign and date the ECG report. The ECG will be repeated only if, in the opinion of the investigator, clinically significant AEs develop during the study that warrants a repeat. The original ECG tracing will be retained in the subject's records at the study site.

9.2. Data Safety Monitoring Board

No Data Safety Monitoring Board is planned for this study.

9.2.1. Appropriateness of Measurements

The efficacy and safety assessments planned for this study are widely used and generally recognized as reliable, accurate, and relevant to the disease condition.

10. STATISTICAL METHODS

10.1. Statistical and Analytical Plans

The primary efficacy, PK, and safety variables and associated analyses are described in this section. Additional details will be described in a statistical analysis plan (SAP) and PK analysis plan that will be prepared and finalized before database lock. Should the analyses specified in the SAP differ from those described in the protocol, the methodology in the SAP will prevail.

General methodology will include descriptive tabular and/or graphical summarizations by randomized treatment group and dose received at the time of assessment, if applicable.

Continuous variables will be presented using descriptive statistics: number of observations (n), mean, standard deviation, standard error of the mean, median, minimum, and maximum values. Categorical values will be summarized with counts and percentages.

All collected data will be presented in listings.

10.2. Datasets or Populations Analyzed

Statistical analyses will be performed on the following populations:

- Full Analysis Set: This population consists of all subjects randomized into the study and receiving at least one dose of correctly assigned study medication.
- PK Population: The PK population consists of all subjects in the study who have at least 1 evaluable PK profile (calculable C_{max} and C_{avg}) and no significant protocol deviations.
- Efficacy Completers Population: This population consists of all subjects in the PK population who have evaluable C_{avg} and C_{max} from the 24-hour PK assessment obtained at Visit 8, Day 90, and no significant protocol deviations.
- Safety population: The safety population consists of all subjects who took at least 1 dose of study drug (SOV2012-F1 or AndroGel).
- ACTH Analysis Set: consists of all subjects randomized into the ACTH substudy.

10.3. Demographic and Other Baseline Characteristics

Descriptive statistical methods will be used to tabulate and summarize demographics and baseline characteristics.

10.4. Efficacy Variables

10.4.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the percentage of SOV2012-F1–treated subjects with a 24-hour total T C_{avg} within the normal range after 90 days of treatment. The Full Analysis Set population will be the primary analysis population.

The C_{avg} will be calculated as area under the concentration-time curve from time 0 to

24 hours (AUC_{0-24}) divided by the actual number of hours between dosing and the 24-hour sample collection time. AUC_{0-24}, AUC_{0-12} and AUC_{12-24} will be calculated using noncompartmental methods. The percentage of subjects randomized to SOV2012-F1 whose 24-hour C_{avg} is within the normal range for total T will be calculated using the Primary Efficacy population. Missing C_{avg} values will be imputed using multiple imputation procedures. The SAP will describe the methodology for multiple imputation in detail.

A 95%, 2-sided, binomial CI surrounding the point estimate will be calculated. The study will have shown effectiveness of SOV2012-F1 if at least 75% of the Full Analysis Set population has total T in the normal range and if the lower bound of the 2-sided 95% CI for that proportion is $\geq 65\%$.

A sensitivity analysis will be performed using the Efficacy Completers population.

Similar analyses of the primary endpoints will be completed for those subjects randomly assigned to receive AndroGel.

10.4.2. Secondary Efficacy Endpoints

10.4.2.1. T C_{max} at Visit 8, Day 90

The key secondary endpoint is the T C_{max} after 90 days of treatment. The Full Analysis Set population analysis will be the primary analysis population. Sensitivity analyses will use the Completers population.

The secondary endpoint will be evaluated by estimating the proportion of SOV2012-F1 treated subjects at Visit 8, Day 90 with:

a) T $C_{max} \leq 1500$ ng/dL

b) T $C_{max} > 1800$ and ≤ 2500 ng/dL

c) T $C_{max} > 2500$ ng/dL

The FDA targets for these PK safety parameters are for a) to be $\geq 85\%$ of subjects, b) to be $< 5\%$ of subjects, and for c) to be no subjects.

Similar analyses of the secondary endpoints will be completed for those subjects randomly assigned to receive AndroGel.

The T levels determined from the plasma T assays processed at inVentiv Health Clinic, Inc. (301D College road East, Princeton, NJ 08540, USA) will be considered the relevant T concentration. In a case where a PK visit is repeated due to loss of sample due to either human error or during transit, the plasma T assay on the repeat PK samples will be considered the relevant T concentration.

10.4.2.2. Pharmacokinetic Assessments

10.4.2.2.1. 24-hour PKAnalysis 10.4.2.2.1.1 SOV2012-F1 Group

The plasma concentrations of T and DHT measured during the 24-hour PK collection days (Days 14, 42, and 90) of study confinement will be listed by subject, by treatment, using the PK Population and summarized with descriptive statistics. These hormone concentrations will be used to derive PK parameters including C_{max}, time to maximum concentration (T_{max}), C_{avg}, and AUC_{0-24} for each 24-hour PK collection day and each subject through noncompartmental analysis. Additional parameters (e.g. area under the concentration-time curve from time 0 to 12 hours [AUC_{0-12}], area under the concentration-time curve from time 12 to 24 hours [AUC_{12-24}], average concentration from time 0 to 12 hours [$C_{avg(0-12)}$], and average concentration from time 12 to 24 hours [$C_{avg(12-24)}$], etc) will be calculated. Actual times will be used to derive PK parameters.

On Day 90, TU and DHTU will also be measured during the 24-hour PK collection. These plasma pro-hormone (TU) and pro-hormone metabolite (DHTU) concentrations will be used to derive PK parameters including C_{max}, T_{max}, C_{avg}, and AUC_{0-24} for each 24-hour PK day and each

subject through noncompartmental analysis. Additional parameters (e.g., AUC_{0-12}, AUC_{12-24}, $C_{avg(0-12)}$, and $C_{avg(12-24)}$, etc) may be calculated if deemed necessary and useful for data interpretation. Actual times will be used to derive PK parameters.

On Day 90, E2 will also be measured during the 24-hour PK collection. These plasma E2 concentrations will be used to derive PK parameters including C_{max}, T_{max}, C_{avg}, and AUC_{0-24} for each subject through noncompartmental analysis. Additional parameters (e.g., AUC_{0-12}, AUC_{12-24}, $C_{avg(0-12)}$, and $C_{avg(12-24)}$, etc) may be calculated if deemed necessary and useful for data interpretation. Actual times will be used to derive PK parameters.

The C_{avg} and AUC_{0-12}, AUC_{12-24} and AUC_{0-24} ratios of DHT to T, and E2 to T normalized by molecular weight, will be calculated and compared between treatments using the PK Population. Each dose titration and changes resulting from dose adjustments (increase/decrease) will be listed and summarized.

Free T concentrations at baseline and for Day 90 24-hour PK timepoints will be calculated using total T, SHBG, and albumin concentrations for each subject according to a validated FTV method [28, 29] with the following equation:

$$FTV = (T - N * FTV) / (K_t(S - T + N * FTV))$$

Where,

- FTV = free T concentration,
- T = total T concentration,
- S = SHBG concentration,
- K_t = association constant of SHBG for T = $5.97 * 10^8$ L/Mol,
- $N = (K_a C_a + 1)$,
  Where,
  - $K_a = 3.6 * 10^4$ L/Mol;
  - C_a = albumin molar concentration (unit in Mol/L).
    For Albumin molar concentration conversion will be: albumin conc. (g/L) divided by 69000 (g/mol) = xx (mol/L).

The units for T and S are nmol/L, while the calculated FTZ will be in nmol/L unit after solving the secondary equation.

Recent research by Friers et al.[30] re-assessed free T calculation using LC/Tandem MS spectrometry with direct equilibrium dialysis method. They found FTV method, although overestimating free T level, appears the most robust approximation, largely independent of SHBG, albumin, and T levels. Therefore, we are changing previously proposed FTZ method to FTV method.

10.4.2.2.2. AndroGel Group

The serum concentrations of T and DHT, and the plasma concentrations of E2 measured at Day 90 of study confinement for AndroGel-treated subjects will be listed by subject, by treatment, and summarized with descriptive statistics using the PK Population. These hormone concentrations will be used to derive PK parameters including C_{max}, T_{max}, C_{avg}, and AUC_{0-24} for 24-hour PK assessment of each subject through noncompartmental analysis.

Additional parameters (e.g., AUC_{0-12}, AUC_{12-24}, $C_{avg[0-12]}$, and $C_{avg[12-24]}$, etc) will be calculated if deemed necessary and useful for data interpretation. Actual times will be used to derive PK parameters.

The C_{avg}, AUC_{0-12}, and AUC_{0-24} ratios of DHT to T and E2 to T normalized by molecular weight, will be also calculated and compared between treatments using the PK Population. Each dose titration and changes resulting from dose adjustments (increase/decrease) will be listed and summarized. Free T concentrations for AndroGel- treated subjects at Day 90 will be calculated using the same FTZ method described in Section 10.4.2.2.1.1.

10.4.2.3. Single PK Timepoint Correlation

Since multiple blood draws over a 24-hour period are not always clinically feasible, it is advantageous to base dose titrations on a single blood draw. The correlation between single PK time points and the mean 24-hour C_{avg} or C_{max} will be explored.

Using the PK Population an exploratory analysis will be performed to correlate 24-hour PK data with a single plasma T concentration measurement, and to confirm a suitable timepoints (e.g. 3 to 5 hours) when the titration outcome based on the single plasma concentration measurement agrees with the titration outcome based on 24-hour PK data the majority of the time. The analysis attempts to further reconfirm titration criteria developed using Phase IIb data on 36 subjects for the clinical label based on these Phase 3 study results.

Detailed PK assessments and analysis methods will be described in the SAP.

10.5. Safety Endpoints

Safety endpoints are:

- Incidence of AEs, SAEs, and AEs leading to study withdrawal in SOV2012-F1–treated subjects compared with AndroGel-treated subjects after 52 weeks of treatment
- Serum cortisol after intravenous administration of synthetic ACTH
- Change from baseline in BP and the following laboratory parameters in SOV2012- F1–treated subjects compared with AndroGel-treated subjects after 52 weeks of treatment:
  - Liver function tests (ALT, AST, total bilirubin, alkaline phosphatase)
  - Hematology parameters (hemoglobin)
  - Hormone levels (LH, FSH, DHT, SHBG, and TSH)
  - Lipid profiles (high-density lipoproteins, low-density lipoproteins, total cholesterol, and triglycerides)
  - Serum PSA

Observed values in vital sign measurements, including sBP, dBP, heart rate, and weight, and changes from baseline in sBP, dBP, and heart rate, will be summarized at each scheduled visit by treatment group and by dose within treatment received at each scheduled collection visit. For sBP, dBP, and heart rate, shift tables for categorical hypertension classifications between

baseline and maximum post baseline values will be presented. The hypertension classifications are defined according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [31] as follows in Table 10-1.

Table 10-1 Hypertension Classifications

Blood Pressure Classification	sBP (mm Hg)	dBP (mm Hg)
Normal	< 120	< 80
Pre-hypertensive	120-139	or 80-89
Stage 1 hypertension	140-159	or 90-99
Stage 2 hypertension	≥ 160	or ≥ 100

Abbreviations: dBP = diastolic blood pressure; sBP = systolic blood pressure.

Occurrences of outlying values of BP and heart rate and their temporal relationship to the maximum dose level of study drug will be explored.

All safety endpoints will be analyzed using the Safety Population except if otherwise defined.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). An AE is considered treatment-emergent if it begins or worsens in severity after the first dose of randomized study drug. For each treatment group, the number and percentage of subjects with treatment-emergent adverse events (TEAEs) will be tabulated by system organ class (SOC) and preferred term. A summary of the number of subjects with TEAEs will be provided by maximum severity as well as by strongest relationship to study drug. Subjects reporting more than 1 AE for a given MedDRA preferred term will be counted only once for that term using the most severe incident/strongest relationship.

Incidence of TEAEs, serious TEAEs, TEAEs resulting in discontinuation from study drug, and TEAEs resulting in death will be summarized by treatment and dose group. Listings will be provided for all AEs, SAEs, and AEs resulting in treatment discontinuation.

Physical examination results will be summarized at each scheduled visit by treatment and dose received at the visit.

Observed values and changes from baseline in laboratory test results will be summarized by treatment and dose within treatment at each scheduled visit. Standard international units will be used for all summaries. Shift tables will be used to evaluate changes in laboratory test values with respect to normal reference ranges. Laboratory tests will be performed at screening and periodically throughout the study and will be summarized.

Actual (observed) values and changes from baseline in continuous biochemistry, hematology, and urinalysis lab parameters will be summarized by treatment group and visit. The number and percentage of subjects with laboratory measurements outside of the normal range will also be summarized by treatment group and visit.

10.5.1. ACTH

ACTH analysis will be performed using the ACTH Analysis Set. Using the maximum increase from pre cosyntropin administration for each of the assessment visits, a mixed- effects model with fixed effects for visit, baseline as a continuous covariate, and subject as a random effect will

be used to analyze the maximum increase from pre cosyntropin administration. Differences in least-squares means of the comparisons between visits (Day 1 and Day 365) will be provided along with the 90% CI's.

10.6. Exploratory Variables

10.6.1. I-PSS, PDQ, SF-36, and IIEF

The observed values and changes from baseline in PDQ, IIEF, SF-36, and I-PSS will be summarized by treatment group and visit. Summaries will be completed separately for those who completed End of Treatment and those whose assessment was completed at the time of Early Withdrawal.

For PDQ, SF-36, and IIEF, the observed values and the change from baseline values will be summarized by treatment group and visit for each subscale or domain score.

I-PSS, PDQ, SF-36, and IIEF summaries will be presented for the safety population. All questionnaire data will also be listed.

The PDQ will be used to assess the subject's sexual function and mood changes. I-PSS is a validated questionnaire used to assess the severity and impact of urinary symptoms. The IIEF is a widely used, multi-dimensional, self-administered investigation that has been found useful in the clinical assessment of erectile dysfunction and treatment outcomes in clinical trials. SF-36 is a set of generic, coherent, and easily administered quality-of-life measures.

These measures rely upon patient self-reporting and are now widely utilized by managed care organizations and by Medicare for routine monitoring and assessment of care outcomes in adult patients.

10.7. Study Drug Exposure and Compliance

Initial study drug dose, titration occurrences (with resultant dose) at scheduled dose adjustment visits, and final study drug dosage will be summarized by treatment group. Duration of treatment in days and cumulative dosage received will be summarized by treatment group. The number of subjects who required interruption, or termination of study drug treatment will be summarized. Compliance will be calculated as the actual number divided by the expected number of doses. These numbers will be determined by tablet counts for the SOV2012-F1 group and the weight of returned bottles for the AndroGel group.

10.8. Medical and Medication History

Medications and a complete medical history will be obtained at screening. These will serve as the baseline for future clinical assessments.

10.9. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the September 2012 World Health Organization Drug Dictionary. Prior medications will be defined as medications documented on the Prior and Concomitant Medications eCRF as having started and stopped before the first dose of any study drug. Concomitant medications will be defined as medications documented on the

Prior and Concomitant Medications eCRF as having started after the start of study drug or having started before the start of study drug and continued on or after the first dose of any study drug. Prior and concomitant medications will be summarized in separate tables.

All concomitant medications administered will be tabulated in a data listing.

10.10. Interim Analyses

Interim analysis of the efficacy data is planned for the 90-Day efficacy period of the study.

10.11. Handling of Missing Data

Missing data for the primary endpoint and key secondary endpoints will be imputed using multiple imputation. The SAP will provide details of the imputation methods.

Missing PK concentrations will generally be considered non-informative; therefore, PK analysis will not impute missing data. Missing actual time points may be replaced with nominal scheduled sample collection times based on case-by-case review.

10.12. Determination of Sample Size

10.12.1. Sample Size Justification

To meet the criterion of the primary endpoint, the proportion of subjects with T C_{avg} within the normal range at Day 90 must be ≥ 75%, with the lower bound of the 95% CI ≥ 65%.

Based on the results of the Phase 2b study, approximately 86% of subjects may be expected to have a T C_{avg} within the normal range at Day 90. The 95% CI associated with different point estimate assumptions are shown in Table 10-2 below. To yield a conservative estimate of the required sample size, the true proportion of subjects with C_{avg} within the normal range is estimated at 75%.

Table 10-2 Sample Size Estimates

Estimated % of Subjects with T C_{avg} in the Eugonadal Range	95% CI	n
75%	(66.5%, 82.3%)	125
80%	(71.9%, 86.6%)	125
82%	(74.1%, 88.3%)	125
85%	(77.5%, 90.8%)	125

Abbreviations: CI = confidence interval; n = number of subjects; T C_{avg} = average plasma total testosterone.

With 125 subjects, the minimal lower limit of 95% Exact (Clopper-Pearson) CI is 66.5%. To account for a potential 17% unevaluable rate during the first 90 days, a total of 151 would have to be randomized into the SOV2012-F1 group.

Additional FDA guidance requires that at least 100 subjects in the oral TU treatment arm reach 12 months of study drug exposure [32]. Assuming a dropout rate of 50% over the course of the 12-month treatment period, 200 subjects would be required to be randomized to the SOV2012-F1 group.

From the results of the Phase 2b study, the T C_{max} has an estimated mean of 1080 and an estimated SD of 341. Under the normal assumption, it is expected to have 0.0016% of subjects with T C_{max} > 2500 mg/dL, 1.7861% of subjects with T C_{max} of 1800 to 2500 mg/dL, and 88.8756% of subjects with T C_{max} < 1500 mg/dL.

In 1000 simulations with 150 subjects, no subjects had T C_{max} >2500 mg/dL. In 15 out of 1000 simulations, the percentage of subjects with T C_{max} of 1800 and 2500 mg/dL is >5%. That is, with a probability of 98.5%, the percentage of subjects with C_{max} of 1800 to 2500 mg/dL is ≤5%. In all 1000 simulations, the percentage of subjects with C_{max} < 1500 mg/dL ranges from 94% to 100%. With a probability of 100%, the percentage of subjects with C_{max} < 1500 mg/dL is ≥85%.

For the ACTH stimulation sub-study, using data from Vestergaard et al. [33] an estimate of intra-subject variability of the data was determined to be approximately 93 nmol/L. As such, for a two-sided 90% confidence interval for a two-sample normal mean difference for a mixed model analysis with subject as a random effect, assuming a common standard deviation of 93 nmol/L, a sample size of 20 per group yields a half width of at most 60 nmol/L with a conditional probability of 0.96 given that the interval contains the true means difference. Assuming an attrition rate of 33% over 12 months, a total of 30 subjects receiving SOV2012-F1 and 15 control subjects taking AndroGel will be enrolled in the sub-study.

10.13. Protocol Deviations

The investigator should not implement any deviation from the protocol without prior review and agreement by the sponsor and in accordance with the IRB and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the investigator must alert one of the following people:

Primary Contact	Alternate Contact
[redacted] Senior Medical Director INC Research, LLC a Syneos Health Company 3201 Beechleaf Court Suite 600 Raleigh, NC 27604-1547 United States [redacted]	[redacted] Chief Medical Officer Marius Pharmaceuticals 8601 Six Forks Road Suite 630 Raleigh, NC 27615-2965 United States [redacted]

Such contact must be made as soon as possible to permit a review by the investigator/sponsor to determine the impact of the deviation on the subject and/or the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IRB, as applicable, before implementation.

Protocol deviations will be listed in the clinical study report.

11. QUALITY ASSURANCE AND QUALITY CONTROL

11.1. Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

11.2. Monitoring

Data for each subject will be recorded on an eCRF. Data collection must be completed for each subject who signs an ICF and is administered study drug.

In accordance with Good Clinical Practice (GCP) and International Council of Harmonisation for Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

The investigator must permit the monitor, the IRB, the sponsor's internal auditors, and representatives from regulatory authorities' direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs.

11.3. Data Management and Coding

INC Research, LLC a Syneos Health Company will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures (SOPs) of the data management and biostatistics departments of INC Research, LLC a Syneos Health Company.

Study centers will enter data directly into an electronic data capture (EDC) system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document.

Any changes to the data entered into the EDC system will be recorded in the audit trail and will be compliant with FDA Code of Federal Regulations (CFR) 21 Part 11.

Medical coding will use MedDRA for concomitant diseases and AEs and World Health Organization Drug Dictionary for medications.

Missing or inconsistent data will be queried in writing to the investigator for clarification. Subsequent modifications to the database will be documented.

12. RECORDS AND SUPPLIES

12.1. Drug Accountability

On receipt of the study drug (including rescue medication, if relevant), the investigator (or deputy) will conduct an inventory of the supplies and verify that study drug supplies are received intact and in the correct amounts before completing a supplies receipt. The investigator will retain a copy of this receipt at the study center and return the original receipt to the study monitor. The monitor may check the study supplies at each study center at any time during the study.

It is the responsibility of the study monitor to ensure that the investigator (or deputy) has correctly documented the amount of the study drug received, dispensed, and returned on the dispensing log that will be provided. A full drug accountability log will be maintained at the study center at all times. The study monitor will arrange collection of unused study drug returned by the subject. The study monitor will also perform an inventory of study drug at the close-out visit to the study center. All discrepancies must be accounted for and documented.

12.2. Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between INC Research, LLC a Syneos Health Company and Marius Pharmaceuticals.

13. ETHICS

13.1. Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

13.2. Regulatory Authorities

Relevant study documentation will be submitted to the FDA for review and approval before the beginning of the study. On completion of the study, regulatory authorities will be notified that the study has ended.

13.3. Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

13.4. Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before that subject has given written informed consent to participate in the study.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject or his authorized representative.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for his further care or penalty or loss of benefits to which he is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the IRB (and regulatory authorities, if required). The study subjects will be informed about this new information and reconsent will be obtained.

13.5. Subject Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IRB approving this research, and the FDA, as well as those of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act, applicable to national and/or local laws and regulations on personal data protection.

14. REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study

(defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor, Marius Pharmaceuticals, or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study-related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The sponsor intends to work with investigators to collectively publish results of the study in a peer-reviewed medical journal where authorship generally will follow level of participation in the study. The sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately.

15. REFERENCES

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16. APPENDICES

16.1. Investigator Signature Page

Protocol Title: A 12-Month, Randomized, Active-controlled, Open-label Study of the Efficacy and Safety of Oral Testosterone Undecanoate in Hypogonadal Men

Protocol Number: MRS-TU-2019

Confidentiality and GCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IRB, I will not modify this protocol without obtaining prior approval of Marius Pharmaceuticals and of the IRB. I will submit the protocol amendments and/or any ICF modifications to Marius Pharmaceuticals and IEC/IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all eCRFs, laboratory samples, or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Marius Pharmaceuticals, to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date

_____

Printed Name

Institution

16.2. Symptoms and Signs Suggestive of Androgen Deficiency in Men

From Endocrine Society 2011:
https://academic.oup.com/jcem/article- lookup/doi/10.1210/jc.2009-2354

Symptoms and signs suggestive of androgen deficiency in men

A. More specific symptoms and signs

- Incomplete or delayed sexual development, eunuchoidism
- Reduced sexual desire (libido) and activity
- Decreased spontaneous erections
- Breast discomfort, gynecomastia
- Loss of body (axillary and pubic) hair, reduced shaving
- Very small (especially <5 ml) or shrinking testes
- Inability to father children, low or zero sperm count
- Height loss, low trauma fracture, low bone mineral density
- Hot flushes, sweats

B. Other less specific symptoms and signs

- Decreased energy, motivation, initiative, and self-confidence
- Feeling sad or blue, depressed mood, dysthymia
- Poor concentration and memory
- Sleep disturbance, increased sleepiness
- Mild anemia (normochromic, normocytic, in the female range)
- Reduced muscle bulk and strength
- Increased body fat, body mass index
- Diminished physical or work performance

16.3. Derivation of Titration Algorithm for SOV2012-F1 (Testosterone Undecanoate 200 mg)

Methods:

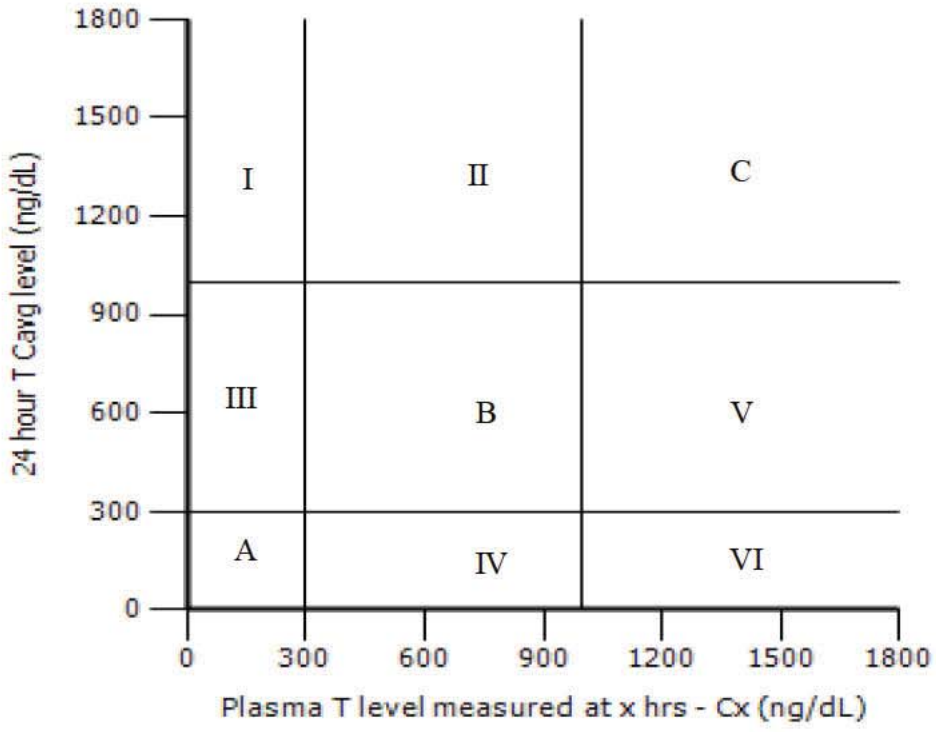
We utilized a similar algorithm from the Axiron product clinical pharmacology review to derive the single blood draw scheme based on data from our Phase IIb trial.

Briefly, we performed comparisons between the titration recommendation made based on the total plasma T concentration (C_x) from a single blood draw and the titration recommendation made based on 24-hour T C_{avg} or C_{max}.

Figure 1 represents the theoretical outcomes (correct or incorrect titration decisions) of using a single blood draw at different time points including 0, 1.5, 3, 4, 5, 6, 8, 10, or 12 hr after morning dosing to predict the 24-hour T C_{avg} as compared to the calculated 24-hour T C_{avg}. For illustrating the approach, this figure uses the commonly accepted serum normal T-range of 300 to 1000 ng/dL.

The regions having discrepancies between Cx-based and 24-hour T C_{avg}-based titration recommendations are defined as "Incorrect" (e.g. regions I - VI), while regions that both titration recommendations agreed are defined as "Correct" (e.g. regions A, B, and C).

Figure 16-1 Theoretical outcomes of Titration Decisions



The percentage of subjects within A, B, and C regions represent the correct titration decisions made from single blood draw plasma T levels; while percentage of subjects within regions I-VI represent incorrect decisions as described as following:

I: Plasma T level less than 300 ng/dL, but the C_{avg} greater than 1000 ng/dL II:

Plasma T level in the normal range, but the C_{avg} greater than 1000 ng/dL III:

Plasma T level less than 300 ng/dL, but the C_{avg} in the normal range IV:

Plasma T level in the normal range, but the C_{avg} less than 300 ng/dL

V: Plasma T level greater than 1000 ng/dL, but the C_{avg} in the normal range VI:

Plasma T level greater than 1000 ng/dL, but the C_{avg} less than 300 ng/dL?

In situations described in I, II, and III, the single blood draw based titration recommendation will result in a dose higher than necessary while in situations described in IV, V, and VI, the single blood draw based titration recommendations will result in a dose lower than necessary.

The same framework applies to C_{max} vs. C_x comparison.

Results

C_{avg}-based decisions

Based on comparisons of 24-hour T C_{avg}-based titration or C_{max}-based titration decisions from Days 7 + 14 of the Phase 2b study combined (400 mg am/400 mg pm regimen only), we found 0, 1.5, 10 and 12 hours are not suitable for making titration decisions while 3-8 hr post morning dose seems to be appropriate range for single blood draw.

Figure 16-2 Percentage of subjects at each time point where use of the blood draw would lead to a correct titration decision (Day 7 and 14 based on 24-hour T Cavg).

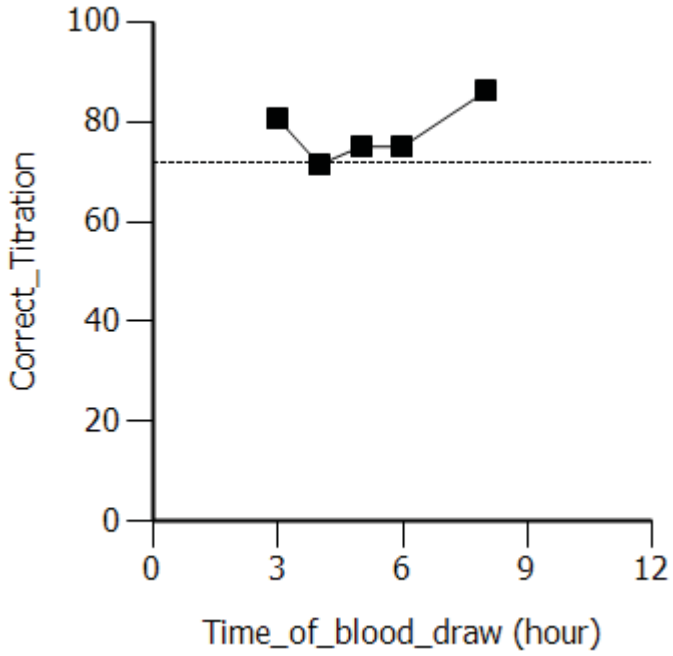


Figure 16-2 suggests that dose titrations based on single blood draws 3-8 hr after morning dosing gives the best match with 24-hour T Cavg-based dose titration recommendations (72-86% correct titration decisions).

Table 16-1 summarizes the occurrence of each unnecessary titration.

Table 16-1 Potentially Incorrect Dose Decisions by Time of Analysis of Plasma Sample (Day 7 and 14)

Time (hr)	3	4	5	6	8
$C_x < C_{avg}$: Unnecessary up-titration (%)	11.1	0	2.8	0	13.9
$C_x > C_{avg}$: Unnecessary down-titration (%)	11.1	25	22.2	19.4	11.1

Figure 16-3 Percentage of Incorrect Titration Decisions based on a Single Blood Draw (Day 7 and 14)

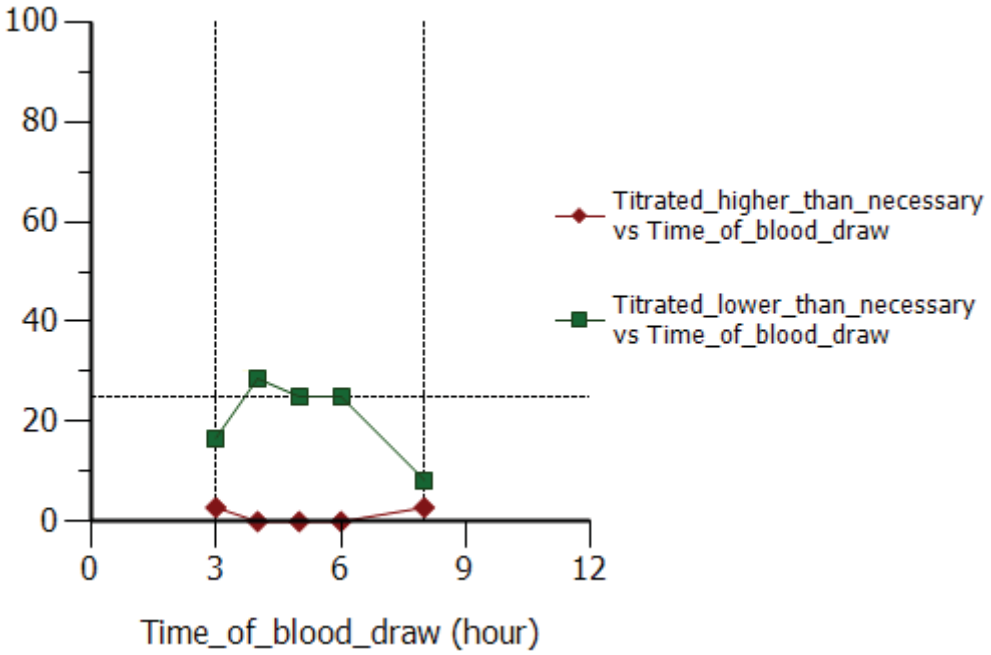


Figure 16-3 illustrates the percentage of incorrect titration decisions based on a single blood draw resulting in doses that were higher or lower than necessary. As Figure 3 suggests, it is reasonable to suggest that subjects should be titrated based on blood draws taken between 3 and 8 hr after morning dose of the drug.

C_{max} -based decisions in combination with C_{avg}

We also compared C_{max} based decisions for the impact of different thresholds for down-titration decisions. Incorporation of C_{max} into the titration algorithm addresses the safety risk of T levels greater than 1500 ng/dL.

Figure 16-4 Percentage of subjects at each time point where use of the blood draw would lead to a correct titration decision (Day 7 and 14 based on Cmax0-12)

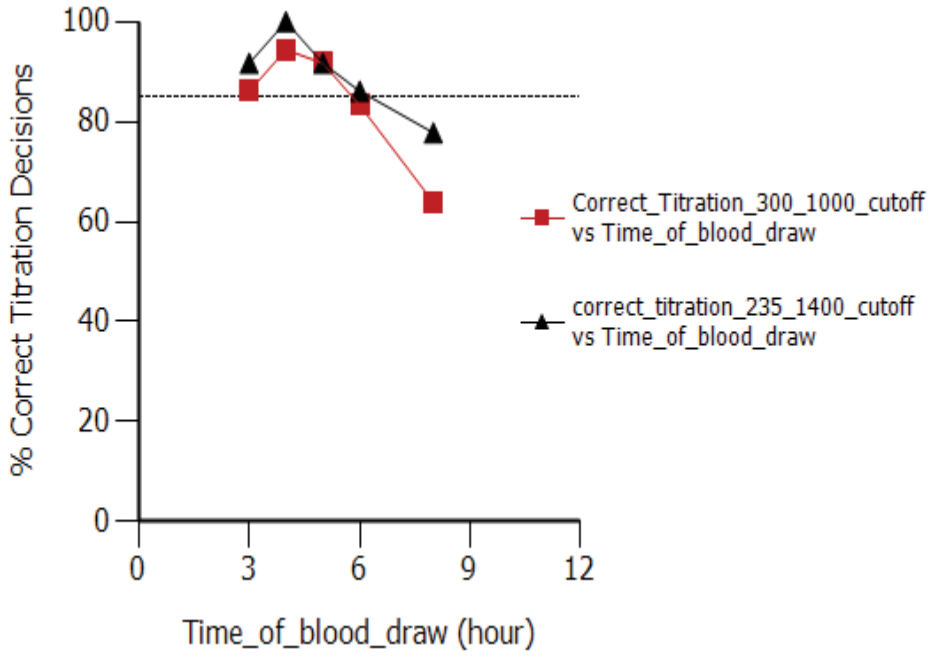


Figure 16-4 suggests that dose titrations based on single blood draws between **3 and 5hr** after morning dosing gives the best match with C_{max}0-12 based dose titration recommendations using the thresholds of 235 and 1400 ng/dL (91.7- 100%). T-values (C_x) below the lower limit of 235 ng/dL results in up-titration to achieve C_{avg} within the normal range. T-values (C_x) above the upper limit of 1400 ng/dL result in down-titration to maintain C_{max} values less than 1500 ng/dL. Application of the range 300-1000 ng/dL resulted in lower correct titration percentages. Additionally, **8 hrs** post morning dosing gives a lower percentage of correct titration decisions, and thus is not recommended. For **6 hr** post morning dosing, we observed 5 subjects in the Phase 2b study having C_{max} over 1600 ng/dL but not meeting down-titration decisions based on plasma T level. Therefore, we propose to use the window of 3-5 hr for our Phase 3 trial.

Table 16-2 Potentially Incorrect Dose Decisions by Time of Analysis of Plasma Sample (Day 7 and 14 data from Phase 2b study).

Cut-off: 300-1000 ng/dL:

Time (hr)	3	4	5	6	8
$C_x < C_{avg}$: Unnecessary up-titration (%)	11.1	0	2.8	8.3	27.8
$C_x > C_{avg}$: Unnecessary down-titration (%)	2.8	5.6	5.6	8.3	8.3

Cut-off: 235-1400 ng/dL:

Time (hr)	3	4	5	6	8
$C_x > C_{avg}$: Unnecessary up-titration (%)	8.3	0	8.3	13.9	22.2
$C_x > C_{avg}$ Unnecessary down-titration (%)	0	0	0	0	0

Table 16-2 confirmed that 6 and 8 hr are not appropriate for single blood draw, and the window of 235-1400 ng/dL provided lower incorrect percentages for both cases.

Therefore, we propose to use 3-5 hr post morning dose as the single blood draw time window. The up- and down-titration thresholds are set at 235 ng/dL and 1400 ng/dL respectively to achieve a high percentage of correct decision while minimizing the percentage of incorrect decisions.

Both Days 49 and 84 in the Phase IIb trial have 24-hour PK data. We evaluated data for these two days on 15 subjects who received 400 mg A.M./200 mg P.M. dose regimen, which is the starting dose in the Phase 3 trial. The proposed titration window of 3-5 hr single blood draw and 235-1400 ng/dL threshold values were validated by this approach.

New cutoff for down-titration decisions

On July 28th, 2017, Marius obtained interim results for Protocol SOV-TNR-2015 (inVentive Protocol 140454) to determine the normal range of testosterone and dihydrotestosterone (DHT) in healthy eugonadal males using our plasma assay. The interim results are for 37 subjects, with a total recruitment of 120 planned for the study. In this normal range study, endogenous T is determined by validated assays using plasma and serum samples obtained from subjects.

Method validation for the plasma method was included in SN0000 for IND 118675. Use of plasma-based samples with an enzyme inhibitor is necessary for reliable measurement of T when an ester-based prodrug such as testosterone undecanoate is used for testosterone replacement therapy.

The interim normal-range study results indicate that assay values for T obtained by the plasma method are **on average 80% of the value of a serum** sample obtained from the same subject at the same time. Both methods use quantitation by LC- MS/MS, and the difference between methods appears consistent across serum testosterone values from 247 to 875 ng/dL (regression analysis yields an R^2 of 0.97).

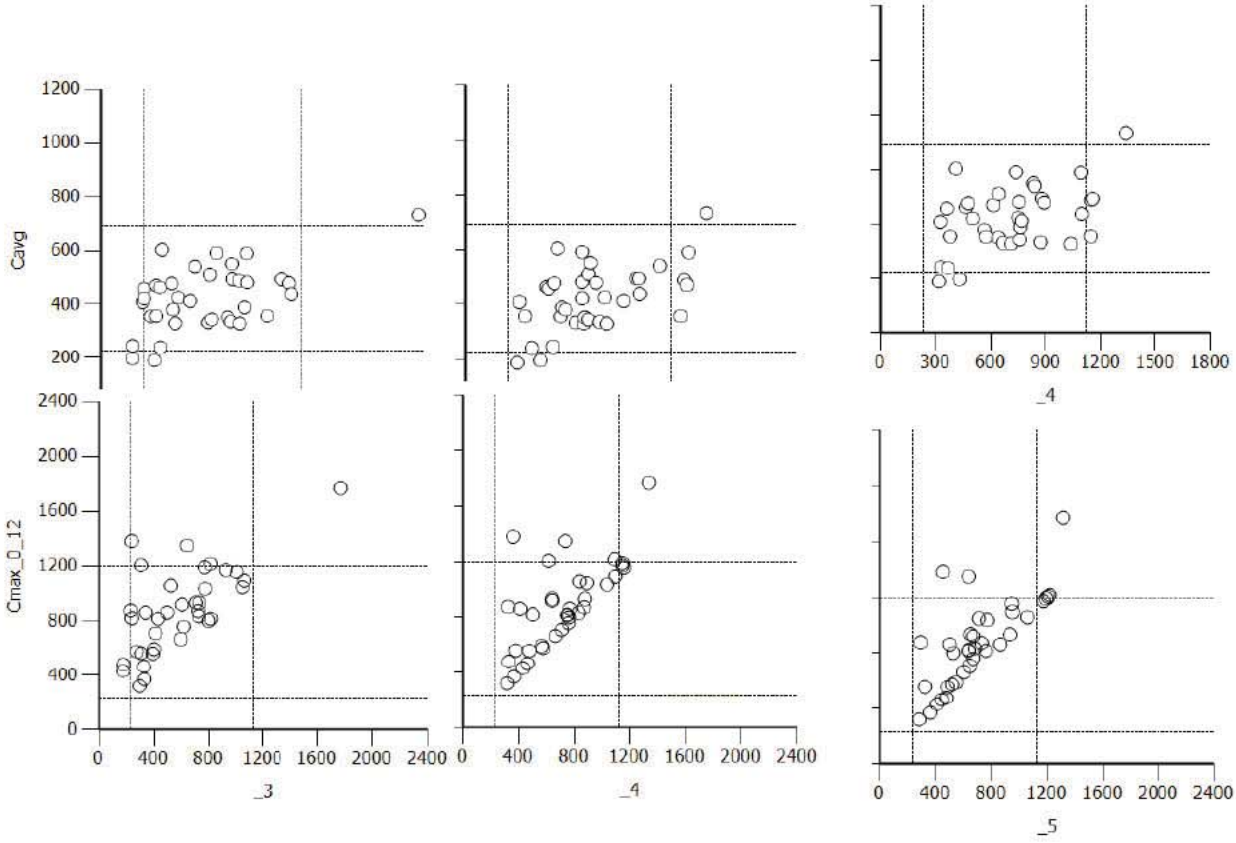
Using these interim results, it appears the normal testosterone range as measured using serum samples would be from about 240 to about 810 ng/dL, and the normal range as measured by the **plasma** method from about **225** to about **690** ng/dL. Although these are interim results, we do not expect the normal ranges or the relationship between plasma and serum results to change materially.

Considering the interim data from the normal range study, we have re-examined the up- and down- titration thresholds. For the up-titration threshold of 235 ng/dL (plasma method), we observe this threshold does approximately correspond to the lower limit of normal range of T-concentrations for the plasma method, estimated at 225 ng/dL based on the interim results of the normal range study. Reviewing the Phase 2b data in view of the emerging normal range results, none of the 15 subjects on the 400/200 mg TU dose would have required up-titration to achieve C_{avg} in the normal range as determined by the plasma method.

With respect to the 1400 ng/dL threshold for triggering down-titration, the observed ratio of plasma to serum results leads us to lower this down-titration threshold to better reflect the normal range as measured by the plasma method. The previous threshold of 1400 will be lowered to 1120 ng/dL (80% of 1400).

We re-evaluated data for both Days 49 and 84 in the Phase IIb on all 36 subjects having 24-hour PK data. The proposed titration window of 3-5 hr single blood draw and 235-1120 ng/dL threshold values are validated.

Figure 16-5 Scatter plot of C_{avg} vs. C_x (Top Row) and C_{max} vs. C_x (Bottom Row) at 3, 4, and 5 hr respectively for 36 subjects in Day 49.



Notes: upper threshold reference line: X=1120 (dashed); lower threshold reference line: X=235 (dashed); reference line for C_{avg}: Y=225 and Y=690 (dashed); C_{max}: Y=225 and Y=1200 (dashed)

Figure 16-5 indicates that single blood draw within 3-5 hr post morning dose using thresholds of 235 and 1120 ng/dL will result in high percentage of correct titrations for both C_{avg}-based (83.3-94.4%) and C_{max}-based decisions (80.6-86.1%), and low percentage of incorrect decisions (5.6-16.7%) which are demonstrated in following Figures 8 and Tables 8.

Figure 16-6 Percentage of subjects at each time point with correct and incorrect titration decisions (Day 49 based on C_{avg} and C_{max}) --- Cutoff 235 – 1120 ng/dL

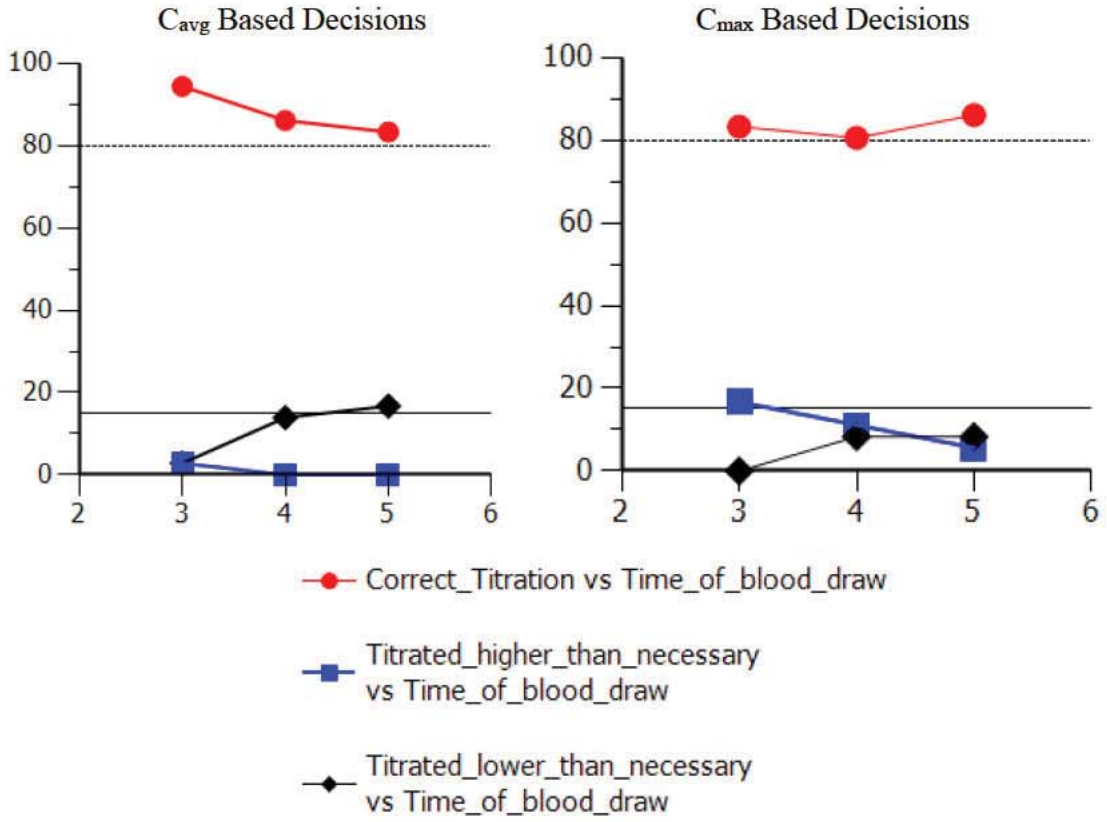


Figure 16-6 suggests that dose titrations based on single blood draws between **3 and 5 hr** after morning dosing gives the best match with 24-hour T Cavg-based dose titration recommendations (94.4%) using single T concentration cut-off 235-1120 ng/dL for titration decisions.

Table 16-3 Potentially Correct and Incorrect Decisions on C_{avg} or C_{max} (Day 49)

Cutoff	C_{avg}-Based Decisions	Description	3 hr	4 hr	5 hr
235 - 1120	Correct Decisions	% of subject	94.4	86.1	83.3
	Incorrect Decisions	Cx < Cavg: Higher titration than necessary (%)	2.8	0	0
		Cx > Cavg: Lower titration than necessary (%)	2.8	13.9	16.7
	C_{max}-Based Decisions				
	Correct Decisions	% of subject	**83.3**	80.6	86.1
	Incorrect Decisions	$C_x < C_{max}$: Higher titration than necessary (%)	16.7	11.1	5.6
		$C_x > C_{max}$: Lower titration than necessary (%)	0	8.3	8.3

Table 16-3 illustrates the percentage of correct titration decisions based on a single blood draw and incorrect titration decisions resulting in doses that were higher or lower than necessary. It is reasonable to suggest that subjects should be titrated based on blood draws taken between **3 and 5 hr** after morning dose of the drug. **(Day 49)** Similar results were also obtained for Day 84.

Titration scheme

In conclusion, we propose that the single blood draw used for titration decisions be obtained 3-5 hr post morning dose. Subjects having single blood draw values of total plasma T less than or equal to 235 ng/dL will be up-titrated. Subjects having single blood draw values of total plasma T greater than 1120 ng/dL will be down-titrated.

The above rationale is incorporated into the protocol for the Phase 3 study, V4.0. Changes are in the Synopsis, and Section 7 (Investigational Plan) and Section 8 (Timing of Study Procedures).

16.4. AndroGel 1.62% Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ANDROGEL 1.62% safely and effectively. See full prescribing information for ANDROGEL 1.62%.

AndroGel® (testosterone gel) 1.62% for topical use CIII
Initial U.S. Approval: 1953

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE
See full prescribing information for complete boxed warning.
- **Virilization has been reported in children who were secondarily exposed to testosterone gel (5.2, 6.2).**
- **Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel (2.2, 5.2).**
- **Healthcare providers should advise patients to strictly adhere to recommended instructions for use (2.2, 5.2, 17).**

RECENT MAJOR CHANGES

Warnings and Precautions (5.6) 10/2016

INDICATIONS AND USAGE
AndroGel 1.62% is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:
- Primary hypogonadism (congenital or acquired) (1)
- Hypogonadotropic hypogonadism (congenital or acquired) (1)

Limitations of use:
- Safety and efficacy of AndroGel 1.62% in men with "age-related hypogonadism" have not been established. (1)
- Safety and efficacy of AndroGel 1.62% in males less than 18 years old have not been established. (1, 8.4)
- Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure. (1, 12.3)

DOSAGE AND ADMINISTRATION
- **Dosage and Administration for AndroGel 1.62% differs from AndroGel 1%. For dosage and administration of AndroGel 1% refer to its full prescribing information. (2)**
- Prior to initiating AndroGel 1.62%, confirm the diagnosis of hypogonadism by ensuring that serum testosterone has been measured in the morning on at least two separate days and that these concentrations are below the normal range (2).
- Starting dose of AndroGel 1.62% is 40.5 mg of testosterone (2 pump actuations or a single 40.5 mg packet), applied topically once daily in the morning. (2.1)
- Apply to clean, dry, intact skin of the shoulders and upper arms. Do not apply AndroGel 1.62% to any other parts of the body including the abdomen, genitals, chest, armpits (axillae), or knees. (2.2, 12.3)
- Dose adjustment: AndroGel 1.62% can be dose adjusted between a minimum of 20.25 mg of testosterone (1 pump actuation or a single 20.25 mg packet) and a maximum of 81 mg of testosterone (4 pump actuations or two 40.5 mg packets). The dose should be titrated based on the pre-dose morning serum testosterone concentration at approximately 14 days and 28 days after starting treatment or following dose adjustment. Additionally, serum testosterone concentration should be assessed periodically thereafter. (2.1)
- Patients should wash hands immediately with soap and water after applying AndroGel 1.62% and cover the application site(s) with clothing after the gel has dried. Wash the application site thoroughly with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated. (2.2)

DOSAGE FORMS AND STRENGTHS
AndroGel (testosterone gel) 1.62% for topical use is available as follows:
- a metered-dose pump that delivers 20.25 mg testosterone per actuation. (3)
- packets containing 20.25 mg testosterone. (3)
- packets containing 40.5 mg testosterone. (3)

CONTRAINDICATIONS
- Men with carcinoma of the breast or known or suspected prostate cancer (4, 5.1)
- Pregnant or breast-feeding women. Testosterone may cause fetal harm (4, 8.1, 8.3)

WARNINGS AND PRECAUTIONS
- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH (5.1)
- Avoid unintentional exposure of women or children to AndroGel 1.62%. Secondary exposure to testosterone can produce signs of virilization. AndroGel 1.62% should be discontinued until the cause of virilization is identified (5.2)
- Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients using testosterone products. Evaluate patients with signs or symptoms consistent with DVT or PE. (5.4)
- Some postmarketing studies have shown an increased risk of myocardial infarction and stroke associated with use of testosterone replacement therapy. (5.5)
- Exogenous administration of androgens may lead to azoospermia (5.8)
- Edema with or without congestive heart failure (CHF) may be a complication in patients with preexisting cardiac, renal, or hepatic disease (5.10)
- Sleep apnea may occur in those with risk factors (5.12)
- Monitor serum testosterone, prostate specific antigen (PSA), hemoglobin, hematocrit, liver function tests and lipid concentrations periodically (5.1, 5.3, 5.9, 5.13)
- AndroGel 1.62% is flammable until dry (5.16)

ADVERSE REACTIONS
The most common adverse reaction (incidence ≥ 5%) is an increase in prostate specific antigen (PSA). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS
- Androgens may decrease blood glucose and therefore may decrease insulin requirements in diabetic patients (7.1)
- Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of International Normalized Ratio (INR) and prothrombin time is recommended (7.2)
- Use of testosterone with adrenocorticotrophic hormone (ACTH) or corticosteroids may result in increased fluid retention. Use with caution, particularly in patients with cardiac, renal, or hepatic disease (7.3)

USE IN SPECIFIC POPULATIONS
There are insufficient long-term safety data in geriatric patients using AndroGel 1.62% to assess the potential risks of cardiovascular disease and prostate cancer. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

- **Virilization has been reported in children who were secondarily exposed to testosterone gel** *[see Warnings and Precautions (5.2) and Adverse Reactions (6.2)]*.
- **Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel** *[see Dosage and Administration (2.2) and Warnings and Precautions (5.2)]*.
- **Healthcare providers should advise patients to strictly adhere to recommended instructions for use** *[see Dosage and Administration (2.2), Warnings and Precautions (5.2) and Patient Counseling Information (17)]*.

1 INDICATIONS AND USAGE

AndroGel 1.62% is indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.
- Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.

Limitations of use:

- Safety and efficacy of AndroGel 1.62% in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.
- Safety and efficacy of AndroGel 1.62% in males less than 18 years old have not been established *[see Use in Specific Populations (8.4)]*.
- Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure *[see Indications and Usage (1), and Clinical Pharmacology (12.3)]*.

2 DOSAGE AND ADMINISTRATION

Dosage and Administration for AndroGel 1.62% differs from AndroGel 1%. For dosage and administration of AndroGel 1% refer to its full prescribing information. (2)

Prior to initiating AndroGel 1.62%, confirm the diagnosis of hypogonadism by ensuring that serum testosterone concentrations have been measured in the morning on at least two separate days and that these serum testosterone concentrations are below the normal range.

2.1 Dosing and Dose Adjustment

The recommended starting dose of AndroGel 1.62% is 40.5 mg of testosterone (2 pump actuations or a single 40.5 mg packet) applied topically once daily in the morning to the shoulders and upper arms.

The dose can be adjusted between a minimum of 20.25 mg of testosterone (1 pump actuation or a single 20.25 mg packet) and a maximum of 81 mg of testosterone (4 pump actuations or two 40.5 mg packets). To ensure proper dosing, the dose should be titrated based on the pre-dose morning serum testosterone concentration from a single blood draw at approximately 14 days and 28 days after starting treatment or following dose adjustment. In addition, serum testosterone concentration should be assessed periodically thereafter. Table 1 describes the dose adjustments required at each titration step.

Table 1: Dose Adjustment Criteria

Pre-Dose Morning Total Serum Testosterone Concentration	Dose Titration
Greater than 750 ng/dL	Decrease daily dose by 20.25 mg (1 pump actuation or the equivalent of one 20.25 mg packet)
Equal to or greater than 350 and equal to or less than 750 ng/dL	No change: continue on current dose
Less than 350 ng/dL	Increase daily dose by 20.25 mg (1 pump actuation or the equivalent of one 20.25 mg packet)

The application site and dose of AndroGel 1.62% are not interchangeable with other topical testosterone products.

2.2 Administration Instructions

AndroGel 1.62% should be applied to clean, dry, intact skin of the upper arms and shoulders. Do not apply AndroGel 1.62% to any other parts of the body, including the abdomen, genitals, chest, armpits (axillae), or knees *[see Clinical Pharmacology (12.3)]*. Area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt. Patients should be instructed to use the palm of the hand to apply AndroGel 1.62% and spread across the maximum surface area as directed in Table 2 (for pump) and Table 3 (for packets) and in Figure 1.

Table 2: Application Sites for AndroGel 1.62%, Pump

Total Dose of Testosterone	Total Pump Actuations	Pump Actuations Per Upper Arm and Shoulder	
		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2
20.25 mg	1	1	0
40.5 mg	2	1	1
60.75 mg	3	2	1

81 mg	4	2	2

Table 3: Application Sites for AndroGel 1.62%, Packets

Total Dose of Testosterone	Total packets	Gel Applications Per Upper Arm and Shoulder	
		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2
20.25 mg	One 20.25 mg packet	One 20.25 mg packet	0
40.5 mg	One 40.5 mg packet	Half of contents of One 40.5 mg packet	Half of contents of One 40.5 mg packet
60.75 mg	One 20.25 mg packet AND One 40.5 mg packet	One 40.5 mg packet	One 20.25 mg packet
81 mg	Two 40.5 mg packets	One 40.5 mg packet	One 40.5 mg packet

The prescribed daily dose of AndroGel 1.62% should be applied to the right and left upper arms and shoulders as shown in the shaded areas in Figure 1.

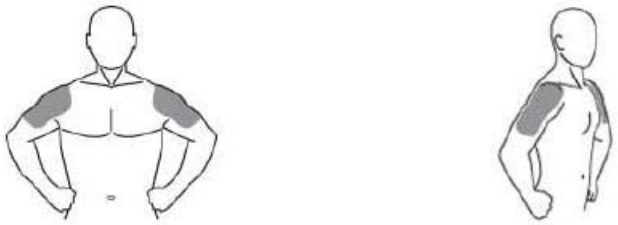


Figure 1. Application Sites for AndroGel 1.62%

Once the application site is dry, the site should be covered with clothing *[see Clinical Pharmacology (12.3)]*. Wash hands thoroughly with soap and water. Avoid fire, flames or smoking until the gel has dried since alcohol based products, including AndroGel 1.62%, are flammable.

The patient should avoid swimming or showering or washing the administration site for a minimum of 2 hours after application *[see Clinical Pharmacology (12.3)]*.

To obtain a full first dose, it is necessary to prime the canister pump. To do so, with the canister in the upright position, slowly and fully depress the actuator three times. Safely discard the gel from the first three actuations. It is only necessary to prime the pump before the first dose.

After the priming procedure, fully depress the actuator once for every 20.25 mg of AndroGel 1.62%. AndroGel 1.62% should be delivered directly into the palm of the hand and then applied to the application sites.

When using packets, the entire contents should be squeezed into the palm of the hand and immediately applied to the application sites. When 40.5 mg packets need to be split between the left and right shoulder, patients may squeeze a portion of the gel from the packet into the palm of the hand and apply to application sites. Repeat until entire contents have been applied. Alternatively, AndroGel 1.62% can be applied directly to the application sites from the pump or packets.

Strict adherence to the following precautions is advised in order to minimize the potential for secondary exposure to testosterone from AndroGel 1.62%-treated skin:

- Children and women should avoid contact with unwashed or unclothed application site(s) of men using AndroGel 1.62%.
- AndroGel 1.62% should only be applied to the upper arms and shoulders. The area of application should be limited to the area that will be covered by a short sleeve t-shirt.
- Patients should wash their hands with soap and water immediately after applying AndroGel 1.62%.
- Patients should cover the application site(s) with clothing (e.g., a t-shirt) after the gel has dried.
- Prior to situations in which direct skin-to-skin contact is anticipated, patients should wash the application site(s) thoroughly with soap and water to remove any testosterone residue.
- In the event that unwashed or unclothed skin to which AndroGel 1.62% has been applied comes in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible.

3 DOSAGE FORMS AND STRENGTHS

AndroGel (testosterone gel) 1.62% for topical use only, is available as follows:

- A metered-dose pump. Each pump actuation delivers 20.25 mg of testosterone in 1.25 g of gel.
- A unit dose packet containing 20.25 mg of testosterone in 1.25 g of gel.
- A unit dose packet containing 40.5 mg of testosterone in 2.5 g of gel.

4 CONTRAINDICATIONS

- AndroGel 1.62% is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.
- AndroGel 1.62% is contraindicated in women who are or may become pregnant, or who are breastfeeding. AndroGel 1.62% may cause fetal harm when administered to a pregnant

woman. AndroGel 1.62% may cause serious adverse reactions in nursing infants. Exposure of a fetus or nursing infant to androgens may result in varying degrees of virilization. Pregnant women or those who may become pregnant need to be aware of the potential for transfer of testosterone from men treated with AndroGel 1.62%. If a pregnant woman is exposed to AndroGel 1.62%, she should be apprised of the potential hazard to the fetus *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Worsening of Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer

- Patients with BPH treated with androgens are at an increased risk for worsening of signs and symptoms of BPH. Monitor patients with BPH for worsening signs and symptoms.
- Patients treated with androgens may be at increased risk for prostate cancer. Evaluation of patients for prostate cancer prior to initiating and during treatment with androgens is appropriate *[see Contraindications (4)]*.

5.2 Potential for Secondary Exposure to Testosterone

Cases of secondary exposure resulting in virilization of children have been reported in postmarketing surveillance of testosterone gel products. Signs and symptoms have included enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases, these signs and symptoms regressed with removal of the exposure to testosterone gel. In a few cases, however, enlarged genitalia did not fully return to age-appropriate normal size, and bone age remained modestly greater than chronological age. The risk of transfer was increased in some of these cases by not adhering to precautions for the appropriate use of the topical testosterone product. Children and women should avoid contact with unwashed or unclothed application sites in men using AndroGel 1.62% *[see Dosage and Administration (2.2), Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)]*.

Inappropriate changes in genital size or development of pubic hair or libido in children, or changes in body hair distribution, significant increase in acne, or other signs of virilization in adult women should be brought to the attention of a physician and the possibility of secondary exposure to testosterone gel should also be brought to the attention of a physician. Testosterone gel should be promptly discontinued until the cause of virilization has been identified.

5.3 Polycythemia

Increases in hematocrit, reflective of increases in red blood cell mass, may require lowering or discontinuation of testosterone. Check hematocrit prior to initiating treatment. It would also be appropriate to re-evaluate the hematocrit 3 to 6 months after starting treatment, and then annually. If hematocrit becomes elevated, stop therapy until hematocrit decreases to an acceptable concentration. An increase in red blood cell mass may increase the risk of thromboembolic events.

5.4 Venous Thromboembolism

There have been postmarketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products such as AndroGel 1.62%. Evaluate patients who report symptoms of pain, edema, warmth and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous thromboembolic event is suspected, discontinue treatment with AndroGel 1.62% and initiate appropriate workup and management *[see Adverse Reactions (6.2)]*.

5.5 Cardiovascular Risk

Long term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiologic studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the use of testosterone compared to non-use. Some studies, but not all, have reported an increased risk of MACE in association with use of testosterone replacement therapy in men.

Patients should be informed of this possible risk when deciding whether to use or to continue to use AndroGel 1.62%.

5.6 Abuse of Testosterone and Monitoring of Serum Testosterone Concentrations

Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids. Anabolic androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions *[see Drug Abuse and Dependence (9)]*.

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

5.7 Use in Women

Due to the lack of controlled evaluations in women and potential virilizing effects, AndroGel 1.62% is not indicated for use in women *[see Contraindications (4) and Use in Specific Populations (8.1, 8.3)]*.

5.8 Potential for Adverse Effects on Spermatogenesis

With large doses of exogenous androgens, including AndroGel 1.62%, spermatogenesis may be suppressed through feedback inhibition of pituitary FSH possibly leading to adverse effects on semen parameters including sperm count.

5.9 Hepatic Adverse Effects

Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g., methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms,

cholestatic hepatitis, and jaundice). Peliosis hepatis can be a life-threatening or fatal complication. Long-term therapy with intramuscular testosterone enanthate has produced multiple hepatic adenomas. AndroGel 1.62% is not known to cause these adverse effects.

5.10 Edema

Androgens, including AndroGel 1.62%, may promote retention of sodium and water. Edema, with or without congestive heart failure, may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease *[see Adverse Reactions (6.2)]*.

5.11 Gynecomastia

Gynecomastia may develop and persist in patients being treated with androgens, including AndroGel 1.62%, for hypogonadism.

5.12 Sleep Apnea

The treatment of hypogonadal men with testosterone may potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung diseases.

5.13 Lipids

Changes in serum lipid profile may require dose adjustment or discontinuation of testosterone therapy.

5.14 Hypercalcemia

Androgens, including AndroGel 1.62 %, should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria). Regular monitoring of serum calcium concentrations is recommended in these patients.

5.15 Decreased Thyroxine-binding Globulin

Androgens, including AndroGel 1.62%, may decrease concentrations of thyroxin-binding globulins, resulting in decreased total T4 serum concentrations and increased resin uptake of T3 and T4. Free thyroid hormone concentrations remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

5.16 Flammability

Alcohol based products, including AndroGel 1.62%, are flammable; therefore, patients should be advised to avoid fire, flame or smoking until the AndroGel 1.62% has dried.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

AndroGel 1.62% was evaluated in a two-phase, 364-day, controlled clinical study. The first phase was a multi-center, randomized, double-blind, parallel-group, placebo-controlled period of 182 days, in which 234 hypogonadal men were treated with AndroGel 1.62% and 40 received placebo. Patients could continue in an open-label, non-comparative, maintenance period for an additional 182 days *[see Clinical Studies (14.1)]*.

The most common adverse reaction reported in the double-blind period was increased prostate specific antigen (PSA) reported in 26 AndroGel 1.62%-treated patients (11.1%). In 17 patients, increased PSA was considered an adverse event by meeting one of the two pre-specified criteria for abnormal PSA values, defined as (1) average serum PSA >4 ng/mL based on two separate determinations, or (2) an average change from baseline in serum PSA of greater than 0.75 ng/mL on two determinations.

During the 182-day, double-blind period of the clinical trial, the mean change in serum PSA value was 0.14 ng/mL for patients receiving AndroGel 1.62% and -0.12 ng/mL for the patients in the placebo group. During the double-blind period, seven patients had a PSA value >4.0 ng/mL, four of these seven patients had PSA less than or equal to 4.0 ng/mL upon repeat testing. The other three patients did not undergo repeat PSA testing.

During the 182-day, open-label period of the study, the mean change in serum PSA values was 0.10 ng/mL for both patients continuing on active therapy and patients transitioning onto active from placebo. During the open-label period, three patients had a serum PSA value > 4.0 ng/mL, two of whom had a serum PSA less than or equal to 4.0 ng/mL upon repeated testing. The other patient did not undergo repeat PSA testing. Among previous placebo patients, 3 of 28 (10.7%), had increased PSA as an adverse event in the open-label period.

Table 4 shows adverse reactions reported by >2% of patients in the 182-day, double-blind period of the AndroGel 1.62% clinical trial and more frequent in the AndroGel 1.62% treated group versus placebo.

Table 4: Adverse Reactions Reported in >2% of Patients in the 182-Day, Double-Blind Period of AndroGel 1.62% Clinical Trial

	Number (%) of Patients	
Adverse Reaction	**AndroGel 1.62% N=234**	**Placebo N=40**
PSA increased*	26 (11.1%)	0%
Emotional lability**	6 (2.6%)	0%
Hypertension	5 (2.1%)	0%
Hematocrit or hemoglobin increased	5 (2.1%)	0%
Contact dermatitis***	5 (2.1%)	0%
**PSA increased* includes: PSA values that met pre-specified criteria for abnormal PSA values (an average change from baseline > 0.75 ng/mL and/or an average PSA value >4.0 ng/mL based on two measurements) as well as those reported as adverse events.		
***Emotional lability* includes: mood swings, affective disorder, impatience, anger, and aggression.		

***Contact dermatitis* includes: 4 patients with dermatitis at non-application sites.

Other adverse reactions occurring in less than or equal to 2% of AndroGel 1.62%-treated patients and more frequently than placebo included: frequent urination, and hyperlipidemia.

In the open-label period of the study (N=191), the most commonly reported adverse reaction (experienced by greater than 2% of patients) was increased PSA (n=13; 6.2%) and sinusitis. Other adverse reactions reported by less than or equal to 2% of patients included increased hemoglobin or hematocrit, hypertension, acne, libido decreased, insomnia, and benign prostatic hypertrophy.

During the 182-day, double-blind period of the clinical trial, 25 AndroGel 1.62%-treated patients (10.7%) discontinued treatment because of adverse reactions. These adverse reactions included 17 patients with PSA increased and 1 report each of: hematocrit increased, blood pressure increased, frequent urination, diarrhea, fatigue, pituitary tumor, dizziness, skin erythema and skin nodule (same patient – neither at application site), vasovagal syncope, and diabetes mellitus. During the 182-day, open-label period, 9 patients discontinued treatment because of adverse reactions. These adverse reactions included 6 reports of PSA increased, 2 of hematocrit increased, and 1 each of triglycerides increased and prostate cancer.

Application Site Reactions

In the 182-day double-blind period of the study, application site reactions were reported in two (2/234; 0.9%) patients receiving AndroGel 1.62%, both of which resolved. Neither of these patients discontinued the study due to application site adverse reactions. In the open-label period of the study, application site reactions were reported in three (3/219; 1.4%) additional patients that were treated with AndroGel 1.62%. None of these subjects were discontinued from the study due to application site reactions.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of AndroGel 1%. Because the reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure (Table 5).

Table 5: Adverse Reactions from Post Approval Experience of AndroGel 1% by System Organ Class

System Organ Class	Adverse Reaction
Blood and lymphatic system disorders:	Elevated hemoglobin or hematocrit, polycythemia, anemia
Cardiovascular disorders:	Myocardial infarction, stroke
Endocrine disorders:	Hirsutism
Gastrointestinal disorders:	Nausea
General disorders:	Asthenia, edema, malaise

Genitourinary disorders:	Impaired urination*
Hepatobiliary disorders:	Abnormal liver function tests
Investigations:	Lab test abnormal**, elevated PSA, electrolyte changes (nitrogen, calcium, potassium [includes hypokalemia], phosphorus, sodium), impaired glucose tolerance, hyperlipidemia, HDL, fluctuating testosterone levels, weight increase
Neoplasms:	Prostate cancer
Nervous system disorders:	Dizziness, headache, insomnia, sleep apnea
Psychiatric disorders:	Amnesia, anxiety, depression, hostility, emotional lability, decreased libido, nervousness
Reproductive system and breast disorders:	Gynecomastia, mastodynia, oligospermia, priapism (frequent or prolonged erections), prostate enlargement, BPH, testis disorder***
Respiratory disorders:	Dyspnea
Skin and subcutaneous tissue disorders:	Acne, alopecia, application site reaction (discolored hair, dry skin, erythema, paresthesia, pruritus, rash), skin dry, pruritus, sweating
Vascular disorders:	Hypertension, vasodilation (hot flushes), venous thromboembolism
* ***Impaired urination*** **includes** nocturia, urinary hesitancy, urinary incontinence, urinary retention, urinary urgency and weak urinary stream	
****Lab test abnormal*** **includes** elevated AST, elevated ALT, elevated testosterone, elevated hemoglobin or hematocrit, elevated cholesterol, elevated cholesterol/LDL ratio, elevated triglycerides, or elevated serum creatinine	
*****Testis disorder*** **includes** atrophy or non-palpable testis, varicocele, testis sensitivity or tenderness	

Secondary Exposure to Testosterone in Children

Cases of secondary exposure to testosterone resulting in virilization of children have been reported in postmarketing surveillance of testosterone gel products. Signs and symptoms of these reported cases have included enlargement of the clitoris (with surgical intervention) or the penis, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases with a reported outcome, these signs and symptoms were reported to have regressed with removal of the testosterone gel exposure. In a few cases, however, enlarged genitalia did not fully return to age appropriate normal size, and bone age remained modestly greater than chronological age. In some of the cases, direct contact with the sites of application on the skin of men using testosterone gel was reported. In at least one reported case, the reporter considered the possibility of secondary exposure from items such as the testosterone gel user's shirts and/or other fabric, such as towels and sheets *[see Warnings and Precautions (5.2)]*.

7 DRUG INTERACTIONS

7.1 Insulin

Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, may decrease insulin requirements.

7.2 Oral Anticoagulants

Changes in anticoagulant activity may be seen with androgens, therefore more frequent monitoring of international normalized ratio (INR) and prothrombin time are recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

7.3 Corticosteroids

The concurrent use of testosterone with adrenocorticotropic hormone (ACTH) or corticosteroids may result in increased fluid retention and requires careful monitoring particularly in patients with cardiac, renal or hepatic disease.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4)]*: AndroGel 1.62% is contraindicated during pregnancy or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. Exposure of a fetus to androgens may result in varying degrees of virilization. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be made aware of the potential hazard to the fetus.

8.3 Nursing Mothers

Although it is not known how much testosterone transfers into human milk, AndroGel 1.62% is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants. Testosterone and other androgens may adversely affect lactation *[see Contraindications (4)]*.

8.4 Pediatric Use

The safety and effectiveness of AndroGel 1.62% in pediatric patients less than 18 years old has not been established. Improper use may result in acceleration of bone age and premature closure of epiphyses.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing AndroGel 1.62% to determine whether efficacy in those over 65 years of age differs from younger subjects. Of the 234 patients enrolled in the clinical trial utilizing AndroGel 1.62%, 21 were over 65 years of age. Additionally, there is insufficient long-term safety data in

geriatric patients to assess the potentially increased risks of cardiovascular disease and prostate cancer.

Geriatric patients treated with androgens may also be at risk for worsening of signs and symptoms of BPH.

8.6 Renal Impairment

No studies were conducted involving patients with renal impairment.

8.7 Hepatic Impairment

No studies were conducted in patients with hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

AndroGel 1.62% contains testosterone, a Schedule III controlled substance in the Controlled Substances Act.

9.2 Abuse

Drug abuse is intentional non-therapeutic use of a drug, even once, for its rewarding psychological and physiological effects. Abuse and misuse of testosterone are seen in male and female adults and adolescents. Testosterone, often in combination with other anabolic androgenic steroids (AAS), and not obtained by prescription through a pharmacy, may be abused by athletes and bodybuilders. There have been reports of misuse by men taking higher doses of legally obtained testosterone than prescribed and continuing testosterone despite adverse events or against medical advice.

Abuse-Related Adverse Reactions

Serious adverse reactions have been reported in individuals who abuse anabolic androgenic steroids and include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, cerebrovascular accident, hepatotoxicity, and serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility and aggression.

The following adverse reactions have also been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidemias, testicular atrophy, subfertility, and infertility.

The following additional adverse reactions have been reported in women: hirsutism, virilization, deepening of voice, clitoral enlargement, breast atrophy, male-pattern baldness, and menstrual irregularities.

The following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth, and precocious puberty.

Because these reactions are reported voluntarily from a population of uncertain size and may include abuse of other agents, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

9.3 Dependence

Behaviors Associated with Addiction

Continued abuse of testosterone and other anabolic steroids, leading to addiction is characterized by the following behaviors:

- Taking greater dosages than prescribed
- Continued drug use despite medical and social problems due to drug use
- Spending significant time to obtain the drug when supplies of the drug are interrupted
- Giving a higher priority to drug use than other obligations
- Having difficulty in discontinuing the drug despite desires and attempts to do so
- Experiencing withdrawal symptoms upon abrupt discontinuation of use

Physical dependence is characterized by withdrawal symptoms after abrupt drug discontinuation or a significant dose reduction of a drug. Individuals taking supratherapeutic doses of testosterone may experience withdrawal symptoms lasting for weeks or months which include depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido and hypogonadotropic hypogonadism.

Drug dependence in individuals using approved doses of testosterone for approved indications has not been documented.

10 OVERDOSAGE

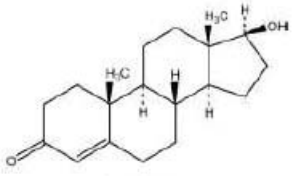
There is a single report of acute overdosage after parenteral administration of an approved testosterone product in the literature. This subject had serum testosterone concentrations of up to 11,400 ng/dL, which were implicated in a cerebrovascular accident. There were no reports of overdosage in the AndroGel 1.62% clinical trial.

Treatment of overdosage would consist of discontinuation of AndroGel 1.62%, washing the application site with soap and water, and appropriate symptomatic and supportive care.

11 DESCRIPTION

AndroGel 1.62% for topical use is a clear, colorless gel containing testosterone. Testosterone is an androgen. AndroGel 1.62% is available in a metered-dose pump or unit dose packets.

The active pharmacologic ingredient in AndroGel 1.62% is testosterone. Testosterone USP is a white to almost white powder chemically described as 17-beta hydroxyandrost-4-en-3-one. The structural formula is:



Testosterone

$C_{19}H_{28}O_2$ MW 288.42

The inactive ingredients in AndroGel 1.62% are: carbopol 980, ethyl alcohol, isopropyl myristate, purified water, and sodium hydroxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement; vocal chord thickening; and alterations in body musculature and fat distribution. Testosterone and DHT are necessary for the normal development of secondary sex characteristics.

Male hypogonadism, a clinical syndrome resulting from insufficient secretion of testosterone, has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (FSH, LH).

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted using AndroGel 1.62%.

12.3 Pharmacokinetics

Absorption

AndroGel 1.62% delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal levels (300 – 1000 ng/dL) seen in healthy men. AndroGel 1.62% provides continuous transdermal delivery of testosterone for 24 hours following once daily application to clean, dry, intact skin of the shoulders and upper arms. Average serum testosterone concentrations over 24 hours (C_{avg}) observed when AndroGel 1.62% was applied to the upper arms/shoulders were comparable to average serum testosterone concentrations (C_{avg}) when AndroGel 1.62% was applied using a rotation method utilizing the abdomen and upper arms/shoulders. The rotation of abdomen and upper arms/shoulders was a method used in the pivotal clinical trial *[see Clinical Studies (14.1)]*.

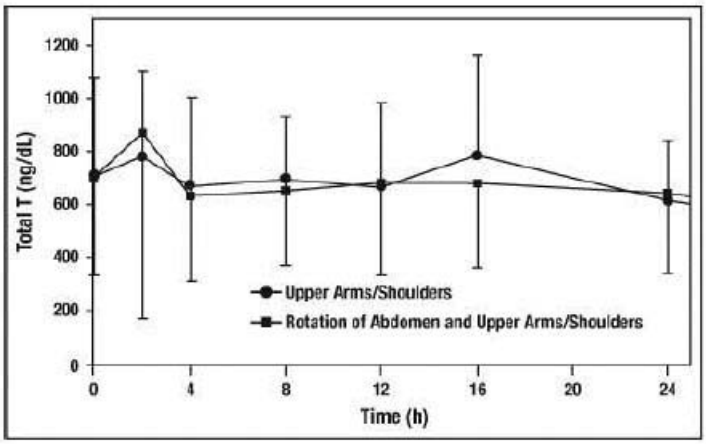


Figure 2: Mean (±SD) Serum Total Testosterone Concentrations on Day 7 in Patients Following AndroGel 1.62% Once-Daily Application of 81 mg of Testosterone (N=33) for 7 Days

Distribution

Circulating testosterone is primarily bound in the serum to sex hormone-binding globulin (SHBG) and albumin. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free) and the rest is loosely bound to albumin and other proteins.

Metabolism

Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and DHT.

Excretion

There is considerable variation in the half-life of testosterone concentration as reported in the literature, ranging from 10 to 100 minutes. About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic acid and sulfuric acid conjugates of testosterone and its metabolites. About 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

When AndroGel 1.62% treatment is discontinued, serum testosterone concentrations return to approximately baseline concentrations within 48-72 hours after administration of the last dose.

Potential for testosterone transfer

The potential for testosterone transfer following administration of AndroGel 1.62% when it was applied only to upper arms/shoulders was evaluated in two clinical studies of males dosed with AndroGel 1.62% and their untreated female partners. In one study, 8 male subjects applied a single dose of AndroGel 1.62% 81 mg to their shoulders and upper arms. Two (2) hours after

application, female subjects rubbed their hands, wrists, arms, and shoulders to the application site of the male subjects for 15 minutes. Serum concentrations of testosterone were monitored in female subjects for 24 hours after contact occurred. After direct skin-to-skin contact with the site of application, mean testosterone C_{avg} and C_{max} in female subjects increased by 280% and 267%, respectively, compared to mean baseline testosterone concentrations. In a second study evaluating transfer of testosterone, 12 male subjects applied a single dose of AndroGel 1.62% 81 mg to their shoulders and upper arms. Two (2) hours after application, female subjects rubbed their hands, wrists, arms, and shoulders to the application site of the male subjects for 15 minutes while the site of application was covered by a t-shirt. When a t-shirt was used to cover the site of application, mean testosterone C_{avg} and C_{max} in female subjects increased by 6% and 11%, respectively, compared to mean baseline testosterone concentrations.

A separate study was conducted to evaluate the potential for testosterone transfer from 16 males dosed with AndroGel 1.62% 81 mg when it was applied to abdomen only for 7 days, a site of application not approved for AndroGel 1.62%. Two (2) hours after application to the males on each day, the female subjects rubbed their abdomens for 15 minutes to the abdomen of the males. The males had covered the application area with a T-shirt. The mean testosterone C_{avg} and C_{max} in female subjects on day 1 increased by 43% and 47%, respectively, compared to mean baseline testosterone concentrations. The mean testosterone C_{avg} and C_{max} in female subjects on day 7 increased by 60% and 58%, respectively, compared to mean baseline testosterone concentrations.

Effect of showering

In a randomized, 3-way (3 treatment periods without washout period) crossover study in 24 hypogonadal men, the effect of showering on testosterone exposure was assessed after once daily application of AndroGel 1.62% 81 mg to upper arms/shoulders for 7 days in each treatment period. On the 7th day of each treatment period, hypogonadal men took a shower with soap and water at either 2, 6, or 10 hours after drug application. The effect of showering at 2 or 6 hours post-dose on Day 7 resulted in 13% and 12% decreases in mean C_{avg}, respectively, compared to Day 6 when no shower was taken after drug application. Showering at 10 hours after drug application had no effect on bioavailability. The amount of testosterone remaining in the outer layers of the skin at the application site on the 7th day was assessed using a tape stripping procedure and was reduced by at least 80% after showering 2-10 hours post-dose compared to on the 6th day when no shower was taken after drug application.

Effect of hand washing

In a randomized, open-label, single-dose, 2-way crossover study in 16 healthy male subjects, the effect of hand washing on the amount of residual testosterone on the hands was evaluated. Subjects used their hands to apply the maximum dose (81 mg testosterone) of AndroGel 1.62% to their upper arms and shoulders. Within 1 minute of applying the gel, subjects either washed or did not wash their hands prior to study personnel wiping the subjects' hands with ethanol dampened gauze pads. The gauze pads were then analyzed for residual testosterone content. A mean (SD) of 0.1 (0.04) mg of residual testosterone (0.12% of the actual applied dose of testosterone, and a 96% reduction compared to when hands were not washed) was recovered after washing hands with water and soap.

Effect of sunscreen or moisturizing lotion on absorption of testosterone

In a randomized, 3-way (3 treatment periods without washout period) crossover study in 18 hypogonadal males, the effect of applying a moisturizing lotion or a sunscreen on the absorption of testosterone was evaluated with the upper arms/shoulders as application sites. For 7 days, moisturizing lotion or sunscreen (SPF 50) was applied daily to the AndroGel 1.62% application site 1 hour after the application of AndroGel 1.62% 40.5 mg. Application of moisturizing lotion increased mean testosterone C_{avg} and C_{max} by 14% and 17%, respectively, compared to AndroGel 1.62% administered alone. Application of sunscreen increased mean testosterone C_{avg} and C_{max} by 8% and 13%, respectively, compared to AndroGel 1.62% applied alone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats. Testosterone was negative in the *in vitro* Ames and in the *in vivo* mouse micronucleus assays. The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

14 CLINICAL STUDIES

14.1 Clinical Trials in Hypogonadal Males

AndroGel 1.62% was evaluated in a multi-center, randomized, double-blind, parallel-group, placebo-controlled study (182-day double-blind period) in 274 hypogonadal men with body mass index (BMI) 18-40 kg/m^2 and 18-80 years of age (mean age 53.8 years). The patients had an average serum testosterone concentration of <300 ng/dL, as determined by two morning samples collected on the same visit. Patients were Caucasian 83%, Black 13%, Asian or Native American 4%. 7.5% of patients were Hispanic.

Patients were randomized to receive active treatment or placebo using a rotation method utilizing the abdomen and upper arms/shoulders for 182 days. All patients were started at a daily dose of 40.5 mg (two pump actuations) AndroGel 1.62% or matching placebo on Day 1 of the study. Patients returned to the clinic on Day 14, Day 28, and Day 42 for predose serum total testosterone assessments. The patient's daily dose was titrated up or down in 20.25 mg increments if the predose serum testosterone value was outside the range of 350-750 ng/dL. The study included four active AndroGel 1.62% doses: 20.25 mg, 40.5 mg, 60.75 mg, and 81 mg daily.

The primary endpoint was the percentage of patients with C_{avg} within the normal range of 300-1000 ng/dL on Day 112. In patients treated with AndroGel 1.62%, 81.6% (146/179) had C_{avg} within the normal range at Day 112. The secondary endpoint was the percentage of patients, with C_{max} above three pre-determined limits. The percentages of patients with C_{max} greater than 1500 ng/dL, and between 1800 and 2499 ng/dL on Day 112 were 11.2% and 5.5%, respectively. Two

patients had a C_{max} >2500 ng/dL on Day 112 (2510 ng/dL and 2550 ng/dL, respectively); neither of these 2 patients demonstrated an abnormal C_{max} on prior or subsequent assessments at the same dose.

Patients could agree to continue in an open-label, active treatment maintenance period of the study for an additional 182 days.

Dose titrations on Days 14, 28, and 42 resulted in final doses of 20.25 mg – 81 mg on Day 112 as shown in Table 6.

Table 6: Mean (SD) Testosterone Concentrations (C_{avg} and C_{max}) by final dose on Days 112 and 364

Parameter	Final Dose on Day 112					
	Placebo (n=27)	20.25 mg (n=12)	40.5 mg (n=34)	60.75 mg (n=54)	81 mg (n=79)	All Active (n=179)
C_{avg} (ng/dL)	303 (135)	457 (275)	524 (228)	643 (285)	537 (240)	561 (259)
C_{max} (ng/dL)	450 (349)	663 (473)	798 (439)	958 (497)	813 (479)	845 (480)
	Final Dose on Day 364					
		20.25 mg (n=7)	40.5 mg (n=26)	60.75 mg (n=29)	81 mg (n=74)	Continuing Active (n=136)
C_{avg} (ng/dL)		386 (130)	474 (176)	513 (222)	432 (186)	455 (192)
C_{max} (ng/dL)		562 (187)	715 (306)	839 (568)	649 (329)	697 (389)

Figure 3 summarizes the pharmacokinetic profile of total testosterone in patients completing 112 days of AndroGel 1.62% treatment administered as a starting dose of 40.5 mg of testosterone (2 pump actuations) for the initial 14 days followed by possible titration according to the follow-up testosterone measurements.

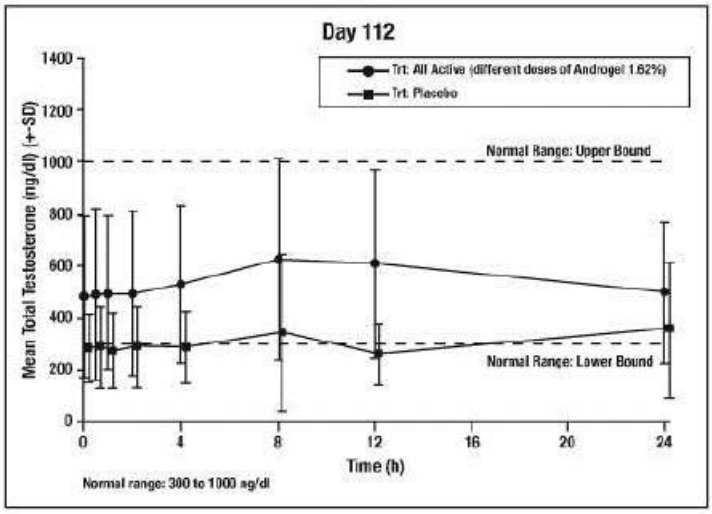


Figure 3: Mean (±SD) Steady-State Serum Total Testosterone Concentrations on Day 112

Efficacy was maintained in the group of men that received AndroGel 1.62% for one full year. In that group, 78% (106/136) had average serum testosterone concentrations in the normal range at Day 364. Figure 4 summarizes the mean total testosterone profile for these patients on Day 364.

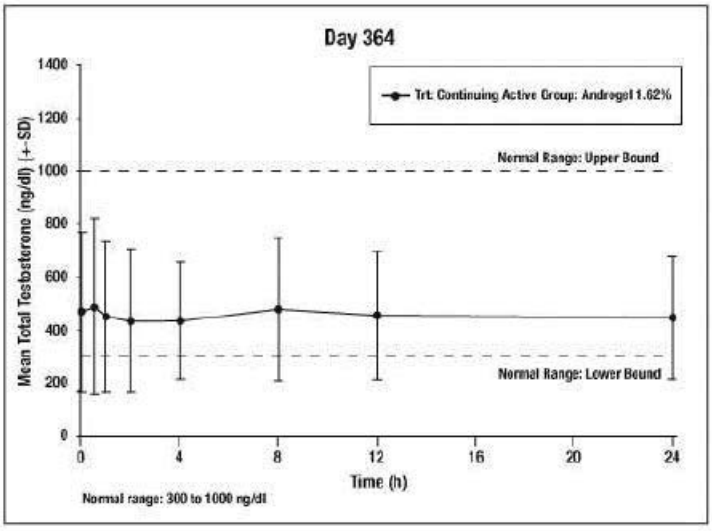


Figure 4: Mean (±SD) Steady-State Serum Total Testosterone Concentrations on Day 364

The mean estradiol and DHT concentration profiles paralleled the changes observed in testosterone. The levels of LH and FSH decreased with testosterone treatment. The decreases in levels of LH and FSH are consistent with reports published in the literature of long-term treatment with testosterone.

16 HOW SUPPLIED/STORAGE AND HANDLING

AndroGel 1.62% is supplied in non-aerosol, metered-dose pumps that deliver 20.25 mg of testosterone per complete pump actuation. The pumps are composed of plastic and stainless steel and an LDPE/aluminum foil inner liner encased in rigid plastic with a polypropylene cap. Each 88 g metered-dose pump is capable of dispensing 75 g of gel or 60-metered pump actuations; each pump actuation dispenses 1.25 g of gel.

AndroGel 1.62% is also supplied in unit-dose aluminum foil packets in cartons of 30. Each packet of 1.25 g or 2.5 g gel contains 20.25 mg or 40.5 mg testosterone, respectively.

NDC Number	Package Size
0051-8462-33	88 g pump (each pump dispenses 60 metered pump actuations with each pump actuation containing 20.25 mg of testosterone in 1.25 g of gel)
0051-8462-12	Each unit dose packet contains 20.25 mg of testosterone provided in 1.25 g of gel
0051-8462-31	30 packets (each unit dose packet contains 20.25 mg of testosterone provided in 1.25 g of gel)
0051-8462-01	Each unit dose packet contains 40.5 mg of testosterone provided in 2.5 g of gel
0051-8462-30	30 packets (each unit dose packet contains 40.5 mg of testosterone provided in 2.5 g of gel)

Store at controlled room temperature 20°-25°C (68°-77°F); excursions permitted to 15°- 30°C (59°- 86°F) [see USP Controlled Room Temperature].

Used AndroGel 1.62% pumps or used AndroGel 1.62% packets should be discarded in household trash in a manner that prevents accidental application or ingestion by children or pets.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Medication Guide

Patients should be informed of the following:

17.1 Use in Men with Known or Suspected Prostate or Breast Cancer

Men with known or suspected prostate or breast cancer should not use AndroGel 1.62% *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

17.2 Potential for Secondary Exposure to Testosterone and Steps to Prevent Secondary Exposure

Secondary exposure to testosterone in children and women can occur with the use of testosterone gel in men. Cases of secondary exposure to testosterone have been reported in children.

Physicians should advise patients of the reported signs and symptoms of secondary exposure, which may include the following:

- In children: unexpected sexual development including inappropriate enlargement of the penis or clitoris, premature development of pubic hair, increased erections, and aggressive behavior.
- In women: changes in hair distribution, increase in acne, or other signs of testosterone effects.
- The possibility of secondary exposure to testosterone gel should be brought to the attention of a healthcare provider.
- AndroGel 1.62% should be promptly discontinued until the cause of virilization is identified.

Strict adherence to the following precautions is advised to minimize the potential for secondary exposure to testosterone from AndroGel 1.62% in men *[see Medication Guide]*:

- **Children and women should avoid contact with unwashed or unclothed application site(s)** of men using AndroGel 1.62%.
- Patients using AndroGel 1.62% should apply the product as directed and strictly adhere to the following:
  - **Wash hands** with soap and water immediately after application.
  - **Cover the application site(s)** with clothing after the gel has dried.
  - **Wash the application site(s) thoroughly** with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated.
- In the event that unwashed or unclothed skin to which AndroGel 1.62% has been applied comes in contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible *[see Dosage and Administration (2.2), Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

17.3 Potential Adverse Reactions with Androgens

Patients should be informed that treatment with androgens may lead to adverse reactions which include:

- Changes in urinary habits such as increased urination at night, trouble starting the urine stream, passing urine many times during the day, having an urge to go to the bathroom right away, having a urine accident, being unable to pass urine and weak urine flow.
- Breathing disturbances, including those associated with sleep, or excessive daytime sleepiness.
- Too frequent or persistent erections of the penis.
- Nausea, vomiting, changes in skin color, or ankle swelling.

17.4 Patients Should Be Advised of the Following Instructions for Use

- **Read the Medication Guide before starting AndroGel 1.62% therapy and to reread it each time the prescription is renewed.**
- **AndroGel 1.62% should be applied and used appropriately to maximize the benefits and to minimize the risk of secondary exposure in children and women.**
- Keep AndroGel 1.62% out of the reach of children.
- **AndroGel 1.62% is an alcohol based product and is flammable; therefore avoid fire, flame or smoking until the gel has dried.**
- It is important to adhere to all recommended monitoring.
- Report any changes in their state of health, such as changes in urinary habits, breathing, sleep, and mood.
- AndroGel 1.62% is prescribed to meet the patient's specific needs; therefore, the patient should never share AndroGel 1.62% with anyone.
- Wait 2 hours before swimming or washing following application of AndroGel 1.62%. This will ensure that the greatest amount of AndroGel 1.62% is absorbed into their system.

Marketed by:

AbbVie Inc.
North Chicago, IL 60064, USA

5036311-Revised October, 2016

Medication Guide

ANDROGEL® (AN DROW JEL) CIII

(testosterone gel) 1.62%

Read this Medication Guide before you start using ANDROGEL 1.62% and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about ANDROGEL 1.62%?

1. **Early signs and symptoms of puberty have happened in young children who were accidentally exposed to testosterone through contact with men using ANDROGEL 1.62%.**

   Signs and symptoms of early puberty in a child may include:
   - enlarged penis or clitoris
   - early development of pubic hair
   - increased erections or sex drive
   - aggressive behavior

   ANDROGEL 1.62% can transfer from your body to others.

2. **Women and children should avoid contact with the unwashed or unclothed area where ANDROGEL 1.62% has been applied to your skin.**

   Stop using ANDROGEL 1.62% and call your healthcare provider right away if you see any signs and symptoms in a child or a woman that may have occurred through accidental exposure to ANDROGEL 1.62%.

   Signs and symptoms of exposure to ANDROGEL 1.62% in children may include:
   - enlarged penis or clitoris
   - early development of pubic hair
   - increased erections or sex drive
   - aggressive behavior

   Signs and symptoms of exposure to ANDROGEL 1.62% in women may include:
   - changes in body hair
   - a large increase in acne

- **To lower the risk of transfer of ANDROGEL 1.62% from your body to others, you should follow these important instructions:**
  - Apply ANDROGEL 1.62% **only** to your shoulders and upper arms that will be covered by a short sleeve t-shirt.
  - Wash your hands **right away** with soap and water after applying ANDROGEL 1.62%.
  - After the gel has dried, **cover the application area with clothing**. Keep the area covered until you have washed the application area well or have showered.
  - **If you expect to have skin-to-skin contact with another person, first wash the application area well with soap and water.**
  - **If a woman or child makes contact with the ANDROGEL 1.62% application area, that area on the woman or child should be washed well with soap and water right away.**

What is ANDROGEL 1.62%?

ANDROGEL 1.62% is a prescription medicine that contains testosterone. ANDROGEL 1.62% is used to treat adult males who have low or no testosterone due to certain medical conditions.

Your healthcare provider will test your blood before you start and while you are taking ANDROGEL 1.62%.

It is not known if AndroGel 1.62% is safe or effective to treat men who have low testosterone due to aging.

It is not known if ANDROGEL 1.62% is safe or effective in children younger than 18 years old. Improper use of ANDROGEL 1.62% may affect bone growth in children.

ANDROGEL 1.62% is a controlled substance (CIII) because it contains testosterone that can be a target for people who abuse prescription medicines. Keep your ANDROGEL 1.62% in a safe place to protect it. Never give your ANDROGEL 1.62% to anyone else, even if they have the

same symptoms you have. Selling or giving away this medicine may harm others and is against the law.

ANDROGEL 1.62% is not meant for use in women.

Who should not use ANDROGEL 1.62%?

Do not use ANDROGEL 1.62% if you:

- have breast cancer
- have or might have prostate cancer
- are pregnant or may become pregnant or are breast-feeding. ANDROGEL 1.62% may harm your unborn or breast-feeding baby.
  Women who are pregnant or who may become pregnant should avoid contact with the area of skin where ANDROGEL 1.62% has been applied.

Talk to your healthcare provider before taking this medicine if you have any of the above conditions.

What should I tell my healthcare provider before using ANDROGEL 1.62%?

Before you use ANDROGEL 1.62%, tell your healthcare provider if you:

- have breast cancer
- have or might have prostate cancer
- have urinary problems due to an enlarged prostate
- have heart problems
- have kidney or liver problems
- have problems breathing while you sleep (sleep apnea)
- have any other medical conditions

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Using ANDROGEL 1.62% with certain other medicines can affect each other.

Especially, tell your healthcare provider if you take:

- insulin
- medicines that decrease blood clotting
- corticosteroids

Know the medicines you take. Ask your healthcare provider or pharmacist for a list of all of your medicines, if you are not sure. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I use ANDROGEL 1.62%?

- It is important that you apply ANDROGEL 1.62% exactly as your healthcare provider tells you to.
- Your healthcare provider will tell you how much ANDROGEL 1.62% to apply and when to apply it.

- Your healthcare provider may change your ANDROGEL 1.62% dose. **Do not** change your ANDROGEL 1.62% dose without talking to your healthcare provider.
- **ANDROGEL 1.62% is to be applied to the area of your shoulders and upper arms that will be covered by a short sleeve t-shirt. Do not** apply ANDROGEL 1.62% to any other parts of your body such as your stomach area (abdomen), penis, scrotum, chest, armpits (axillae), or knees.
- Apply ANDROGEL 1.62% at the same time each morning. ANDROGEL 1.62% should be applied after showering or bathing.
- **Wash your hands right away** with soap and water after applying ANDROGEL 1.62%.
- Avoid showering, swimming or bathing for at least 2 hours after you apply ANDROGEL 1.62%.
- ANDROGEL 1.62% is flammable until dry. Let ANDROGEL 1.62% dry before smoking or going near an open flame.
- Let the application site dry completely before putting on a t-shirt.

Applying ANDROGEL 1.62%:

ANDROGEL 1.62% comes in a pump or in packets.

- **Before applying ANDROGEL 1.62% make sure that your shoulders and upper arms are clean, dry, and that there is no broken skin.**
- The application sites for ANDROGEL 1.62% are the upper arms and shoulders that will be covered by a short sleeve t-shirt (See Figure A).

(Figure A)

If you are using ANDROGEL 1.62% pump:

- Before using a new bottle of ANDROGEL 1.62 % for the first time, you will need to prime the pump. To prime the ANDROGEL 1.62% pump, slowly push the pump all the way down 3 times. **Do not** use any ANDROGEL 1.62% that came out while priming. Wash it down the sink to avoid accidental exposure to others. Your ANDROGEL 1.62% pump is now ready to use.
- Remove the cap from the pump. Then, position the nozzle over the palm of your hand and slowly push the pump all the way down. Apply ANDROGEL 1.62% to the application site. You may also apply ANDROGEL 1.62% directly to the application site.
- **Wash your hands with soap and water right away.**

Find Your Dose as Prescribed by Your Healthcare Provider		Application Method
1 PUMP DEPRESSION	20.25 mg	Apply 1 pump depression of ANDROGEL 1.62% to 1 upper arm and shoulder.
2 PUMP DEPRESSIONS	40.5 mg	Apply 1 pump depression of ANDROGEL 1.62% to 1 upper arm and shoulder and then apply 1 pump depression of ANDROGEL 1.62% to the opposite upper arm and shoulder.
3 PUMP DEPRESSIONS	60.75 mg	Apply 2 pump depressions of ANDROGEL 1.62% to 1 upper arm and shoulder and then apply 1 pump depression of ANDROGEL 1.62% to the opposite upper arm and shoulder.
4 PUMP DEPRESSIONS	81 mg	Apply 2 pump depressions of ANDROGEL 1.62% to 1 upper arm and shoulder and then apply 2 pump depressions of ANDROGEL 1.62% to the opposite upper arm and shoulder.

If you are using ANDROGEL 1.62% packets:

- Tear open the packet completely at the dotted line. Squeeze from the bottom of the packet to the top.
- Squeeze all of the ANDROGEL 1.62% out of the packet into the palm of your hand. Apply ANDROGEL 1.62% to the application site. You may also apply ANDROGEL 1.62% directly to the application site.
- ANDROGEL 1.62% should be applied right away.
- **Wash your hands with soap and water right away.**

Find Your Dose as Prescribed by Your Healthcare Provider		Application Method
One 20.25 mg packet	20.25 mg	Apply 1 packet of ANDROGEL 1.62% to 1 upper arm and shoulder.
One 40.5 mg packet	40.5 mg	Apply half of the 40.5 mg packet of ANDROGEL 1.62% to 1 upper arm and shoulder and then apply the remaining packet contents to the opposite upper arm and shoulder.
One 40.5 mg packet and one 20.25 mg packet	60.75 mg	Apply one 40.5 mg packet of ANDROGEL 1.62% to 1 upper arm and shoulder and then apply one 20.25 mg packet of ANDROGEL 1.62% to the opposite upper arm and shoulder.
Two 40.5 mg packets	81 mg	Apply one 40.5 mg packet of ANDROGEL 1.62% to 1 upper arm and shoulder and then apply one 40.5 mg packet of ANDROGEL 1.62% to the opposite upper arm and shoulder.

What are the possible side effects of ANDROGEL 1.62%?

See "What is the most important information I should know about ANDROGEL 1.62%?"

ANDROGEL 1.62% can cause serious side effects including:

- **If you already have enlargement of your prostate gland your signs and symptoms can get worse while using ANDROGEL 1.62%.** This can include:
  - increased urination at night
  - trouble starting your urine stream
  - having to pass urine many times during the day
  - having an urge that you have to go to the bathroom right away
  - having a urine accident
  - being unable to pass urine or weak urine flow
- **Possible increased risk of prostate cancer.** Your healthcare provider should check you for prostate cancer or any other prostate problems before you start and while you use ANDROGEL 1.62%.
- **Blood clots in the legs or lungs.** Signs and symptoms of a blood clot in your leg can include leg pain, swelling, or redness. Signs and symptoms of a blood clot in your lungs can include difficulty breathing or chest pain.
- **Possible increased risk of heart attack or stroke.**
- **In large doses ANDROGEL 1.62% may lower your sperm count.**
- **Swelling of your ankles, feet, or body, with or without heart failure.**
- **Enlarged or painful breasts.**
- **Have problems breathing while you sleep (sleep apnea).**

Call your healthcare provider right away if you have any of the serious side effects listed above.

The most common side effects of ANDROGEL 1.62% include:

- increased prostate specific antigen (a test used to screen for prostate cancer)
- mood swings
- hypertension
- increased red blood cell count
- skin irritation where ANDROGEL 1.62% is applied

Other side effects include more erections than are normal for you or erections that last a long time.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ANDROGEL 1.62%. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ANDROGEL 1.62%?

- Store ANDROGEL 1.62% at 59°F to 86°F (15°C to 30°C).
- When it is time to throw away the pump or packets, safely throw away used ANDROGEL 1.62% in household trash. Be careful to prevent accidental exposure of children or pets.
- Keep ANDROGEL 1.62% away from fire.

Keep ANDROGEL 1.62% and all medicines out of the reach of children.

General information about the safe and effective use of ANDROGEL 1.62%

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ANDROGEL 1.62% for a condition for which it was not prescribed. Do not give ANDROGEL 1.62% to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about ANDROGEL 1.62%. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about ANDROGEL 1.62% that is written for health professionals.

For more information, go to www.androgel.com or call 1-800-633-9110.

What are the ingredients in ANDROGEL 1.62%?

Active ingredient: testosterone

Inactive ingredients: carbopol 980, ethyl alcohol, isopropyl myristate, purified water and sodium hydroxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Marketed by:

AbbVie Inc.
North Chicago, IL 60064, USA

5036311-Revised October, 2016

16.5. International Prostate Symptom Score

URINARY SYMPTOM SCORE

International prostate symptom score (IPPS) for men

NAME:

DATE:

PLEASE CIRCLE THE BEST ANSWER AS IT APPLIES TO YOUR CURRENT CONDITION. OPTIONS (LEGEND) ARE THE SAME FOR QUESTIONS 1-5.

1. **Incomplete emptying**
   Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?

   0 = not at all 1 = less than 1 time in 5 2 = less than _ the time
   3 = about _ the time 4 = more than _ the time 5 = almost always

2. **Frequency**
   Over the past month, how often have you had to urinate again less than two hours after you finished urinating? 0 1 2 3 4 5

3. **Intermittency**
   Over the past month, how often have you found you stopped and started again several times when you urinated? 0 1 2 3 4 5

4. **Urgency**
   Over the past month, how often have you found it difficult to postpone urination? 0 1 2 3 4 5

5. **Weak stream**
   Over the past month, how often have you had a weak urinary stream? 0 1 2 3 4 5

6. **Straining**
   Over the post month, how often have you had to push or strain to begin urination? 0 1 2 3 4 5

7. **Nocturia**
   a. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?

   0 = none 1 = 1 time 2 = 2 times 3 = 3 times
   4 = 4 times 5 = 5 times or more

YOUR TOTAL SCORE = _____.

Quality of life due to urinary symptoms
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?

0 = delighted	2 = mostly satisfied	4 = mostly dissatisfied	
1 = pleased	3 = mixed	5 = unhappy	6 = terrible

SYMPTOM SCORE SEVERITY:

MILD (symptom score ≤ 7)
MODERATRE (symptom score range 8-19)
SEVERE (symptom score range 20-35)

Source: American Urological Association

Version downloaded from www.urospec.com/uro/Forms/ipss.pdf 25 April 2017

16.6. Psychosexual Daily Questionnaire

Psychosexual Daily Questionnaire

(a) Center No.: ☐ (b) Subject No.: ☐ (c) Visit No.: ☐ (d) Day: ☐ (e) Date: ☐

1. Please rate your overall level of sexual desire today by circling the appropriate number below:

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7
none (0) · very low (1) · very high (7)

2. Please rate highest level of enjoyment or pleasure of any sexual activity that you experienced today.
(a) without a partner (e.g., masturbationl sexual fantasies) and/or (b) with a partner (e.g., kissing, intercourse) by circling the appropriate number below.

(a) Without a partner: 0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 (none … very high enjoyment/pleasure)

(b) With a partner: 0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 (none … very high enjoyment/pleasure)

(c) Please indicate if partner is available ☐ yes ☐ no

3. Please rate your mood by writing the number that corresponds to the scale below. For each item 0 indicates that the descriptor is not at all true; 7 indicates that the descriptor is very true for you today.

not at all true 0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 very true

(a) Angry? ___	(d) Full of pep/energetic?___	(g) Friendly?_____
(b) Alert? ___	(e) Sad or Blue?_____	(h) Nervous?_____
(c) Irritable?___	(f) Tired? _____	(i) Well/good?_____

4. For all of the items below check yes if you have experienced (or are experiencing) today, otherwise check no.

	Yes	No		Yes	No		Yes	No	
(a)	☐	☐	sexual daydreams	☐	☐	orgasm	☐	☐	masturbation
(b)	☐	☐	anticipation of sex	☐	☐	flirting (by others toward you)	☐	☐	night spontaneous erection
(c)	☐	☐	sexual interactions with partner	☐	☐	ejaculation	☐	☐	day spontaneous erection
(d)	☐	☐	flirting (by you)	☐	☐	intercourse	☐	☐	erection in response to sexual activity

Answer the following two questions only if you experienced an erection as shown in No. 4. j-l above.

5. If you experienced an erection today, indicate the % full erection that you experienced by circling the appropriate number below (make a reasonable estimate):

%= 0 10 20 30 40 50 60 70 80 90 100

6. If you experienced an erection today, indicate whether it was maintained for a satisfactory duration by circling the appropriate number below:

not satisfactory 0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 very satisfactory

Day is the relative day of the reporting period/week (i.e., 1,2,3,4,5,6, or 7)

Source: Division of Endocrinology, Harbor-UCLA Research and Education Institute, Journal of Andrology, September/October 2013

16.7. Short Form Survey

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
☐1	☐2	☐3	☐4	☐5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
▼	▼	▼	▼	▼
☐1	☐2	☐3	☐4	☐5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐1	☐2	☐3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1	☐2	☐3
c. Lifting or carrying groceries	☐1	☐2	☐3
d. Climbing several flights of stairs	☐1	☐2	☐3
e. Climbing one flight of stairs	☐1	☐2	☐3
f. Bending, kneeling, or stooping	☐1	☐2	☐3
g. Walking more than a mile	☐1	☐2	☐3
h. Walking several blocks	☐1	☐2	☐3
i. Walking one block	☐1	☐2	☐3
j. Bathing or dressing yourself	☐1	☐2	☐3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2
b. Accomplished less than you would like	☐ 1	☐ 2
c. Were limited in the kind of work or other activities	☐ 1	☐ 2
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2
b. Accomplished less than you would like	☐ 1	☐ 2
c. Did work or other activities less carefully than usual	☐ 1	☐ 2

6. **During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. **How much bodily pain have you had during the past 4 weeks?**

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

8. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of pep?	☐1	☐2	☐3	☐4	☐5	☐6
b. Have you been a very nervous person?	☐1	☐2	☐3	☐4	☐5	☐6
c. Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5	☐6
d. Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5	☐6
e. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5	☐6
f. Have you felt downhearted and blue?	☐1	☐2	☐3	☐4	☐5	☐6
g. Did you feel worn out?	☐1	☐2	☐3	☐4	☐5	☐6
h. Have you been a happy person?	☐1	☐2	☐3	☐4	☐5	☐6
i. Did you feel tired?	☐1	☐2	☐3	☐4	☐5	☐6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b. I am as healthy as anybody I know	☐1	☐2	☐3	☐4	☐5
c. I expect my health to get worse	☐1	☐2	☐3	☐4	☐5
d. My health is excellent	☐1	☐2	☐3	☐4	☐5

Thank you for completing these questions!

16.8. International Index of Erectile Function Questionnaire

IIEF: International Index of Erectile Function Questionnaire

Investigator: _____

Date of Visit: _____

Instructions:

These questions ask about the effects your erection problems have had on your sex life, over the past 4 weeks. Please answer the following questions as honestly and clearly as possible. In answering these questions, the following definitions apply:

Definitions:

- Sexual activity includes intercourse, caressing, foreplay and masturbation.
- Sexual intercourse is defined as vaginal penetration of the partner (you entered the partner).
- Sexual stimulation includes situations like foreplay with a partner, looking at erotic pictures, etc.
- Ejaculate is defined as the ejection of semen from the penis (or the feeling of this).

Mark ONLY one circle per question. Please use an X where applicable and be sure to initial and date all corrections.

1. Over the past 4 weeks, how often were you able to get an erection during sexual activity?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (much more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (much less than half the time)
- ☐ Almost never or never

2. Over the past 4 weeks, when you had erections with sexual stimulation, how often were your erections hard enough for penetration?

- ☐ No sexual stimulation
- ☐ Almost always or always
- ☐ Most times (much more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (much less than half the time)
- ☐ Almost never or never

Questions 3, 4 and 5 will ask about erections you may have had during sexual intercourse.

3. Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?

- Did not attempt intercourse
- Almost always or always
- Most times (much more than half the time)
- Sometimes (about half the time)
- A few times (much less than half the time)
- Almost never or never

4. Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

- Did not attempt intercourse
- Almost always or always
- Most times (much more than half the time)
- Sometimes (about half the time)
- A few times (much less than half the time)
- Almost never or never

5. Over the past 4 weeks, during sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

- Did not attempt intercourse
- Almost always or always
- Most times (much more than half the time)
- Sometimes (about half the time)
- A few times (much less than half the time)
- Almost never or never

6. Over the past 4 weeks, how many times have you attempted sexual intercourse?

- No attempts
- 1-2 attempts
- 3-4 attempts
- 5-6 attempts
- 7-10 attempts
- 11 or more attempts

7. Over the past 4 weeks, when you attempted sexual intercourse how often was it satisfactory for you?

- Did not attempt intercourse
- Almost always or always

- Most times (much more than half the time)
- Sometimes (about half the time)
- A few times (much less than half the time)
- Almost never or never

8. Over the past 4 weeks, how much have you enjoyed sexual intercourse?

- No intercourse
- Very highly enjoyable
- Highly enjoyable
- Fairly enjoyable
- Not very enjoyable
- Not enjoyable

9. Over the past 4 weeks, when you had sexual stimulation or intercourse how often did you ejaculate?

- Did not attempt intercourse
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (much less than half the time)
- Almost never or never

10. Over the past 4 weeks, when you had sexual stimulation or intercourse how often did you have the feeling of orgasm or climax (with or without ejaculation)?

- No sexual stimulation or intercourse
- Almost always or always
- Most times (much more than half the time)
- Sometimes (about half the time)
- A few times (much less than half the time)
- Almost never or never

Questions 11 and 12 ask about sexual desire. Let's define sexual desire as a feeling that may include wanting to have a sexual experience (for example, masturbation or intercourse), thinking about having sex or feeling frustrated due to a lack of sex.

11. Over the past 4 weeks, how often have you felt sexual desire?

- Almost always or always
- Most times (much more than half the time)
- Sometimes (about half the time)

- A few times (much less than half the time)
- Almost never or never

12. Over the past 4 weeks, how would you rate your level of sexual desire?

- Very high
- High
- Moderate
- Low
- Very low or none at all

13. Over the past 4 weeks, how satisfied have you been with you overall sex life?

- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

14. Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?

- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

15. Over the past 4 weeks, how do you rate your confidence that you can get and keep your erection?

- Very high
- High
- Moderate
- Low
- Very low

Source: Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF) a multidimensional scale for assessment of erectile dysfunction. Urology. 1997 Jun; 49(6):822-30.

16.9. Amount of Blood Drawn per Study Day, SOV2012-F1 Group

Blood volumes shown in the following table are approximate. Additional blood samples may be taken if needed to follow up on individual subject safety.

For subjects participating in the ACTH stimulation sub-study, an additional 10.5 mL of blood volume will be collected at Day 1 and Day 365.

	Time	PK			Chem	Hem	Endo	Lipids and PSA	Others
		T (serum)	E2 (plasma)	TU & DHTU (plasma)					
	(hr)	(mL)	(mL)	(mL)	(mL)	(mL)	(mL)	(mL)	(mL)
Screening 1	–	3	–	–	–	–	–	–	–
Screening 2	–	Included in Chem	–	–	8.5	3	3.5	2.5	–
Treatment		**Plasma PK**							
		T & DHT	E2	TU & DHTU					
Day 1	Pre- morning dose	4	7	–	8.5	3	3.5	2.5	2
Day 14	Pre- morning dose	4	–	–	8.5	–	–	2.5	2
	1.5	4	–	–	–	–	–	–	–
	3	4	–	–	–	–	–	–	–
	4	4	–	–	–	–	–	–	–
	5	4	–	–	–	–	–	–	–
	6	4	–	–	–	–	–	–	–
	8	4	–	–	–	–	–	–	–
	12 (pre-evening dose)	4	–	–	–	–	–	–	–
	13.5	4	–	–	–	–	–	–	–
	15	4	–	–	–	–	–	–	–
	16	4	–	–	–	–	–	–	–
	17	4	–	–	–	–	–	–	–
	18	4	–	–	–	–	–	–	–
	20	4	–	–	–	–	–	–	–
	24	4	–	–	–	–	–	–	–
Day 42	Pre- morning dose	4	–	–	8.5	–	–	2.5	2
	1.5	4	–	–	–	–	–	–	–
	3	4	–	–	–	–	–	–	–
	4	4	–	–	–	–	–	–	–
	5	4	–	–	–	–	–	–	–
	6	4	–	–	–	–	–	–	–
	8	4	–	–	–	–	–	–	–
	12 (pre-evening dose)	4	–	–	–	–	–	–	–
	15	4	–	–	–	–	–	–	–
	16	4	–	–	–	–	–	–	–
	17	4	–	–	–	–	–	–	–
	18	4	–	–	–	–	–	–	–
	20	4	–	–	–	–	–	–	–
	24	4	–	–	–	–	–	–	–
Day 90	Pre- morning dose	4	7	2	8.5	3	3.5	2.5	2
	1.5	4	7	2	–	–	–	–	–
	3	4	7	2	–	–	–	–	–

	4	4	7	2	–	–	–	–	–
	5	4	7	2	–	–	–	–	–
	6	4	7	2	–	–	–	–	–
	8	4	7	2	–	–	–	–	–
	12 (pre-evening dose)	4	7	2	–	–	–	–	–
	13.5	4	7	2	–	–	–	–	–
	15	4	7	2	–	–	–	–	–
	16	4	7	2	–	–	–	–	–
	17	4	7	2	–	–	–	–	–
	18	4	7	2	–	–	–	–	–
	20	4	7	2	–	–	–	–	–
	24	4	7	2	–	–	–	–	–
Day 166	Single blood draw postdose	4	–	–	–	–	–	–	–
Day 180	Pre- morning dose	–	–	–	8.5	3	–	2.5	2
Day 256	Single blood draw postdose	4	–	–	–	–	–	–	–
Day 270	Pre- morning dose	–	–	–	8.5	3	–	2.5	2
Day 365	Pre- morning dose	–	–	–	8.5	3	3.5	2.5	2
	Single blood draw postdose	4	–	–	–	–	–	–	–
Subtotal (mL)		199	112	30	68	18	14	20	14
Total (mL)									**475**
Day 180 or Day 270 (at least 12 subjects)	**Bio-analytical Stability Study**								**168***
V7E through V16E Extension	**MRS-TU-2019EXT ABPM Extension**								495**
Serum T Substudy at V12E/D90E	**MRS-TU-2019EXT**								52.5***

Abbreviations: Chem = chemistry; Endo =endocrinology; Hem = hematology; hr = hour; Id = identification; Others = fasting insulin and fasting plasma glucose; PK = pharmacokinetic; PSA = prostate-specific antigen.
* Total study volume for Bioanalytical Sample Stability Substudy will be 475 + 168 = 643 mL.
**Total study volume for ongoing Subjects in MRS-TU-2019EXT, not otherwise participating in the Bioanalytical Substudy, the total blood volume will be 475+ 495= 970 mL.
***Total study volume for ongoing Subjects in MRS-TU-2019EXT, not otherwise having participated in the Bioanalytical Substudy but participating in the V12E/D90E Serum T substudy, the total blood volume will be 495mL + 52.5= 547.5 mL.

16.10. Amount of Blood Drawn per Study Day, AndroGel Group

Blood volumes shown in the following table are approximate. Additional blood samples may be taken if needed to follow up on individual subject safety.

	Time	PK		Chem	Hem	Endo	Lipid and PSA	Others
		T (serum)	E2 (plasma)					
	(hr)	(mL)	(mL)	(mL)	(mL)	(mL)	(mL)	(mL)
Screening 1	–	3	–	–	–	–	–	–
Screening 2	–	Included in Chem	–	8.5	3	3.5	2.5	–
Treatment		T & DHT (serum)	E2 (plasma)					
Day 1	Pre- morning dose	4	7	8.5	3	3.5	2.5	2
Day 14	Pre- morning dose	4	–	8.5	–	–	2.5	2
Day 42	Pre- morning dose	4	–	8.5	–	–	2.5	2
Day 90	Pre- morning dose	4	7	8.5	3	3.5	2.5	2
	2	4	7	–	–	–	–	–
	4	4	7	–	–	–	–	–
	8	4	7	–	–	–	–	–
	12	4	7	–	–	–	–	–
	16	4	7	–	–	–	–	–
	20	4	7	–	–	–	–	–
	24	4	7	–	–	–	–	–
Day 166	Pre- morning dose	4	–	–	–	–	–	–
Day 180	Pre- morning dose	–	–	8.5	3	–	2.5	2
Day 256	Pre- morning dose	4	–	–	–	–	–	–
Day 270	Pre- morning dose	–	–	8.5	3	–	2.5	2
Day 365	Pre- morning dose	4	–	8.5	3	3.5	2.5	2
Subtotal (mL)		59	63	68	18	14	20	14
Total (mL)								**256**

Abbreviations: Chem = chemistry; Endo = endocrinology; Hem = hematology; hr = hour; Id = identification; Others = fasting insulin and fasting plasma glucose; PK = pharmacokinetic; PSA = prostate-specific antigen.

16.11. Lack of stability of hematocrit measurement as a function of age of sample

During the first month of screening patients for the study of oral testosterone undecanoate in hypogonadal patients (Protocol MRS-TU-2019), Marius has observed an elevated ratio of hematocrit (HCT) to hemoglobin (HGB). Where a typical HCT:HGB ratio is around 3.0, the mean ratio in the patients screened to date is 3.3, with 39% (66 of 171 subjects screened) of men exceeding the maximum allowable HCT (48%). Of these men with high hematocrit values, only four had HGB concentrations greater than 16 g/dL.

In discussing this issue with BARC Laboratories, it became clear that this problem is due to the known increase in mean corpuscular volume and hematocrit during storage[1]. This problem does not exist with HGB results. The following table illustrates data generated by BARC:

Table 16-4 Laboratory Value Changes with Sample Age at Room Temperature

BARC XE 5000 TIME STUDY
SPECIMENS LEFT AT ROOM TEMP FOR 5 DAYS.

DAY		WBC	RBC	HGB	HCT	MCV	MCH	MCHC
1		4.94	4.87	15.3	44.1	90.6	31.4	34.7
2		4.34	5.22	15.9	48.1	92.1	30.5	33.1
3		4.77	4.95	15.5	48	97	31.3	32.3
4		4.63	4.92	15.5	49.3	100.2	31.5	31.4
5		4.38	4.89	15.4	50.8	103.9	31.5	30.3

Because the laboratory evaluations in the study are done centrally, the measurements are not performed until at least 24 hours after a blood sample is drawn. Whole blood samples are shipped at ambient temperature.

Because of this artefactual increase in HCT result, one that increases with storage time, Marius has elected to revise its inclusion and exclusion criteria to solely reflect HGB values. Men entering the trial must have a HGB concentration between 11.0 and 16.0 g/dL if they have not received testosterone supplementation in the previous 30 days, or between 11.0 and 17.0 g/dL if prior testosterone therapy was stopped in the previous 30 days (because of the known effect of testosterone to increase HCT). Because of variability in sample storage/shipping time between collection and measurement, HCT results will no longer be reported, but estimated as 3 times the HGB value. This approach to the measurement of blood counts is consistent with what was done in the NIH-sponsored Testosterone Trials (TTrials; ClinicalTrials.gov identifier NCT00799617).

[1]Cohle SD, Saleem A, Makkaoui DE. Effects of storage of blood on stability of hematologic parameters. Am J Clin Pathol 76:67-9, 1981.

16.12. MRS-TU-2019EXT ABPM Extension Synopsis

A. OVERVIEW

Protocol Title
MRS-TU-2019EXT Ambulatory Blood Pressure Monitoring (ABPM) Extension Study

Study Centers
Up to 32 of the 35 MRS-TU-2019 sites in United States

Introduction
Study MRS-TU-2019EXT is an extension to study MRS-TU-2019. One purpose is to further examine the blood pressure (BP) effects of Marius's oral testosterone undecanoate formulation, SOV2012-F1, using 24-hour ambulatory blood pressure monitoring (ABPM). Another primary objective will be to demonstrate the feasibility of using a lower starting dose of SOV2012-F1 (daily dose of 400 mg [200 mg with breakfast meal and 200mg with dinner meal]) to titrate individual doses in order to further enhance drug administration.

Eligible subjects will include up to approximately 170 men who complete the 52-week MRS-TU-2019 study and are willing to consent to participate in the extension study. Eligible men who have consented to this extension study will be withdrawn from testosterone replacement therapy for a minimum of 8 weeks following their conclusion of MRS-TU-2019.

Late Entry Subjects from MRS-TU-2019:

Subjects who completed Day 365 in MRS-TU-2019 prior to the start of MRS-TU-2019EXT, may enroll in MRS-TU-2019EXT, bypassing the Day 364-365 ABPM extension study requirement. These late entry subjects will still be required to have an 8-week washout period, beginning at time of consent. *Any interim testosterone therapy between time of completion of MRS-TU-2019 and consent for MRS-TU-2019EXT, must be recorded in the electronic case report form.* As with other participating subjects, they must pass the ABPM evaluation at V7E/ Day 1E to continue in the ABPM extension study.

New Subject Enrollment into Extension Study*: Enrollment of patients naïve to MRS-TU-2019 or subjects who have completed the main study MRS-TU-2019 ≥ 8 weeks ago, will be permitted at a few sites in order to maximize enrollment for MRS-TU-2019EXT, provided those patients meet both the main study and extension study eligibility criteria. These subjects* ***would be required to consent and then complete screening assessments of the Screening Visit 1(EXT) and Screening Visit 2 (EXT),*** *for assessments consistent with the main protocol, prior to being enrolled into MRS-TU-2019EXT.* ***See 16.12.2 Schedule of Assessments, ABPM Extension Study Pre-Treatment Period: For Newly Enrolled Subjects (MRS-TU-2019 naïve or Late Entry subjects who qualify for new enrollment due to extended time off study).***

Subjects completing the main study, MRS-TU-2019 and going directly into MRS-TU-2019EXT, complete the extension study defined 8-week washout, and begin a total of 180 days of treatment on SOV2012-F1. *Late Entry Subjects* (subjects having a gap between completion of main study and entry into the MRS-TU-2019EXT study) will complete 8 weeks of additional washout from time of consent and then begin 180 days of treatment on SOV2012F1. *For newly enrolled subjects in MRS-TU-2019EXT*, see modified Schedule of Assessments in Section 16.12.2, for washout and pre-treatment screening requirements.

During the 180-day treatment period, subjects will be titrated up or down, if necessary, over the first 4 to 8 weeks (28 to 56 days) of treatment period using a refined dose-titration algorithm. Subjects will stay on their final dose from Day 28 or Day 56, through Day 180, the completion of the ABPM study. ABPM will be conducted 3-4 times during the MRS-TU-2019EXT study depending on whether the subject rolls onto the extension study directly from MRS-TU-2019, or is a MRS-TU-2019EXT Late Entry Subject, or a New Subject Enrollment participant*: at EOT main study, after 8 weeks washout, at month 4 and at month 6 of treatment. The 6-month visit will provide data on stabilization of ambulatory BP, following the 4-month data for ambulatory BP primary endpoint.

The design provides the advantage of being able to evaluate the durability of observed BP changes by obtaining ABPM data from the SOV2012-F1 and Androgel study subjects after long term (i.e. 365 days) treatment. In the MRS-TU-2019 study, the increase in in-clinic BP appears to be maximal within 6 weeks of starting androgen replacement therapy with SOV2012- F1. In MRS-TU-2019EXT, an 8-week washout of androgen replacement therapy was chosen to conservatively re-establish a treatment-free baseline BP. To confirm that a steady state of BP is reached by 8 weeks after androgen withdrawal, in-clinic blood pressure will be measured after 4, 6, 7 and 8 weeks of androgen withdrawal. The achievement of steady state will be determined by repeated measures analysis that will look at the slope of the line relative to days 6, 7, and 8 and provide 90% confidence intervals (CIs) around the slope.

24-hr Serum T/DHT Substudy:

At select centers, approximately 100 subjects will participate in a 24-hr Serum T sample collection substudy. Subjects enrolled in the Serum T substudy should have Serum T samples drawn at all PK timepoints: pre-morning dose and 1.5, 3, 4, 5, 6, 8, 12, 13.5, 15, 16, 17, 18, 20, and 24 hours after AM dose. These samples will be stored at the central laboratory for exploratory analysis, related to the disease and the investigational product under study.

B. OBJECTIVES

Primary Objective

- To assess change from baseline in 24-hour mean systolic blood pressure (sBP) measured by ABPM after approximately 120 (±3) days of treatment, in SOV2012-F1–treated subjects.
- To determine the response to a lower starting dose of oral SOV2012-F1 with up and down titration as appropriate, as measured by:
    - The percentage of SOV2012-F1–treated subjects with average plasma total testosterone (T Cavg) within the normal range after 90 days of treatment.

Secondary Objectives

- To determine the response to a lower starting dose of oral SOV2012-F1 with up and down titration as appropriate, as measured by:

  The percentage of SOV2012-F1–treated subjects after 90 days of treatment with maximum plasma testosterone concentration (T Cmax) values

  < 1500 ng/dL;

  > 1800 to ≤ 2500 ng/dL;

  > 2500 ng/dL.

- To assess change from baseline in 24-hour mean systolic blood pressure (sBP) measured by ABPM after approximately 180 (±3) days of treatment, in SOV2012-F1–treated subjects.
- To assess change from baseline in 24-hour mean diastolic blood pressure (dBP) measured by ABPM after 120 (±3) days and 180 (±3) days of treatment, in SOV2012-F1–treated subjects. To assess change from baseline in 24-hour heart rate (HR) measured by ABPM, after 120 (±3) days and 180 (±3) days of treatment, in SOV2012-F1–treated subjects.
- To assess change from baseline in BP and HR measured in clinic after 120 (±3) and 180 (±3) days of treatment, in SOV2012-F1–treated subjects.
- To collect samples for bioanalysis to correlate endogenous T levels (following medication washout) obtained in serum and plasma tubes (EDTA and NaF/EDTA).

Safety Objectives

- To assess hematology parameters, hormone levels, lipid profiles, and serum prostate-specific antigen (PSA) in SOV2012-F1–treated subjects after 180 days of treatment.
- To determine the incidence of adverse events (AEs), serious adverse events (SAEs), and AEs leading to study withdrawal in SOV2012-F1-treated subjects after 180 days of treatment.

C. AMBULATORY BLOOD PRESSURE MONITORING (ABPM) EXTENSION (E) STUDY DESIGN

The MRS-TU-2019 ABPM Extension Study (MRS-TU-2019EXT), will extend the participation for up to 170 MRS-TU-2019 subjects to enroll into the MRS-TU-2019EXT, for a target of 135 evaluable subjects reaching the 4-month ABPM assessment.

MRS-TU-2019 Continuation Subjects:

For subjects not having yet completed MRS-TU-2019, the first 24-hr ABPM assessment is at Day 365/EOT and will serve as a historical control of BP levels following long-term treatment with MRS-TU-2019.

For this group, the second 24-hr ABPM session will occur at V7E/Day 1E, following an 8-week washout of the EOT study medication for MRS-TU-2019(or washout of any interim use of testosterone replacement medication). This second "washed out" 24-hr ABPM assessment session will serve as the baseline for ABPM values moving forward. *Subjects are required to pass the Visit 7E/Day 1E ABPM assessment session with successful collection of 24-hr data in order to continue in the MRS-TU-2019EXT study.*

For this group, the third and fourth24-hr ABPM assessment sessions will occur at Day 120 days and Day180 (±3) of treatment with SOV2012-F1. These assessments will be primarily evaluated in comparison to the baseline obtained at the Visit 7E/Day 1E session, and secondarily to the first 24-hr session performed at the EOT in MRS-TU- 2019.

Late Entry Subjects to MRS-TU-2019EXT:

For subjects already having completed D365 of MRS-TU-2019 prior to the start of MRS- TU-2019EXT, there is a late entry pathway for them to enroll into the ABPM EXT study. Subjects in this group will bypass the D364-365 ABPM visit requirement and have their first ABPM visit at Visit 7E/D1E following their consent and the subsequent 8-week washout. *Any interim testosterone therapy between time of completion of MRS-TU-2019 and consent for MRS-TU-2019EXT, must be recorded in the electronic case report form.*

***New Subject Enrollment into MRS-TU-2019EXT**:*

Enrollment of patients naïve to MRS-TU-2019 will be permitted at a few sites in order to maximize enrollment for MRS-TU-2019EXT, provided those patients meet both the main study and extension study eligibility criteria. These subjects ***would be required to consent and then complete screening assessments of the Screening Visit 1 (EXT) and Screening Visit 2 (EXT), consistent with the main protocol, prior to being enrolled into MRS-TU-2019EXT**.*

***Subjects who would otherwise be considered Late Entry Subjects from the main study MRS-TU-2019 and who completed the main study ≥8 weeks before the start of MRS-TU-2019EXT, may be considered for new subject screening** and enter the MRS-TU-2019EXT by way of the new enrollment subject pathway, thereby avoiding an additional 8-week washout period.*

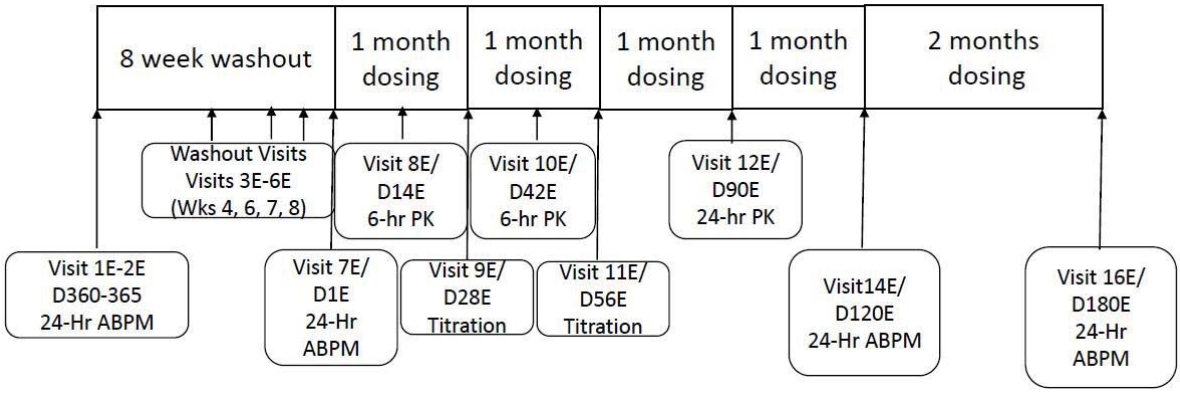
Before selecting patients for new enrollment screening, assure that at minimum, they meet the MRS-TU-2019EXT criteria before bringing the patient in for lab test screening.

***See 16.12.2 Schedule of Assessments Pre-Treatment Period,** ABPM Extension Study Pre-Treatment Period: For Newly Enrolled Subjects (MRS-TU-2019 naïve or Late Entry Subjects who qualify for New Enrollment).*

As with other participating subjects, **they must pass the ABPM evaluation at V7E/D1E to continue in the ABPM extension study.**

Each ABPM session requires a visit for hook up of the ambulatory BP recorder, with patient education (or refresher) and a visit 24 hours later for removal of the recorder and data download. See Section F, **Schedule of Assessments: ABPM Extension Study**.

The following diagram illustrates the design for subjects moving from MRS-TU-2019 directly to MRS-TU-2019EXT*:



***For Late Entry Subjects and New Subject Enrollees,** a modified study entry schedule is provided. See Schedule of Assessments 16.12.1 to 16.12.3):

Once completing the 24-hour ABPM data download successfully at the end of the washout period, extension study subjects will begin 180-days of open label treatment with SOV2012-F1, at the starting daily dose of 400 mg (200 mg AM and 200 mg PM). See Section F **Schedule of Assessments: ABPM Extension Study** for timing of visits and relevant visit windows.

During the 180-day treatment period of the extension study, the plasma T concentration between 3 to 5 hours on Day 14E and Day 42E will determine the need, if any, to adjust the dose up or down at Day 28E and Day 56E, respectively. The minimum dose of SOV2012- F1 will be 100 mg once a day with breakfast. The maximum dose of SOV2012-F1 will be 800 mg (as 400 mg BID with breakfast and with dinner). By Day28 or Day 56E the subject will reach a stable dose for the remainder of the 180-day treatment period.

Titration decisions will be communicated through the same Interactive Web Response Technology (IWRT) system used in MRS-TU-2019.

Clinical Blood Pressure (BP) and Heart Rate (HR) Assessment Procedure

In order to standardize in-clinic BP assessments, HR and BP will be measured between 7 AM and 9 AM and should be assessed at approximately the same time at each visit for individual subjects (within ± 60 mins). The BP measurements during the extension study will be obtained using an automated digital BP device at each clinic visit, using a cuff and bladder assembly appropriate to the size of the subject's arm according to American Heart Association (AHA) guidelines (Hypertension. 2005; 45:142-161).
Beginning with Visit 2E / Day 365, BP at all visits during the MRS-TU-2019EXT study should be collected using the subject's non-dominant arm. The subject should be sitting for at least 5 mins prior to measuring BP, and the arm should be extended and supported at the level of the heart (mid-chest height).
Blood Pressure should be obtained in triplicate, 1 min (+5min) apart, while subject is seated and arm is extended and supported at the level of the heart (mid-chest height).
The same BP cuff should be used across all subsequent visits. *Likewise, the non-dominant arm should be used for ABPM monitoring and the subject should be advised accordingly. The subject should not smoke within 30 min of the start of the study visit when obtaining vital signs.*

ABPM Procedure

In addition to the in-clinic BP monitoring in the MRS-TU-2019 study and the MRS-TU-2019EXT study, ambulatory blood pressure will be collected in this extension study, for the purpose of evaluating pharmacodynamic changes in BP and heart rate over 24 hours.

Use of ABPM is expected to provide additional data on how BP changes from pre-treatment, in the typical daily subject environment. The ABPM procedure is outlined as follows:

- A portable, automated BP monitoring device, with inflatable cuff supported by a shoulder strap or belt will be hooked up on the subject at the 3 or 4 designated visits.
- The subject will be trained on the practical use of the ABPM device before the subject leaves the clinic, with instructions to return the next day.
- The electronically pre-programmed ABPM recorder will be set up to inflate in 30- min increments throughout the daytime hours (7 AM to 11 PM) and in 30- min increments during the night time hours (11 PM to 7 AM).

  At Visit 7E/ Day 1E, if the 24-hr ABPM assessment is considered to "fail", based on pre- specified quality control requirements, the subject will be requested to repeat the 24-hr ABPM session within 2 days of the initially failed ABPM session.

  If the repeat 24-hr ABPM session fails to meet the technical requirements for a successful session at Visit 7E/ Day 1E, the subject will be withdrawn from the MRS-TU-2019EXT study.
- A preliminary download of ABPM session data will be immediately available to the site study coordinator upon the subject returning to the clinic with the recorder. This preliminary data will be used to determine the quality of the 24-hr ABPM assessment session, and whether a repeat of the 24-hr ABPM process is required for the subject. Criteria constituting a failed set of ABPM 24-hr data is defined as any of the following:
  - More than 10 of the required 48 timepoints over 24 hours are missing/unreadable (> 20%)
  - >2 consecutive hours of data missing (5 or more consecutive 30- min data points missing).
  - Less than 22 hours of recording time

D. BIOANALYTICAL SAMPLE COLLECTION

Blood samples for the bioanalytical objective will be collected following 8 weeks of study medication washout at visit 7E (on Day 1E prior to dosing). Collection tubes will be supplied by the central laboratory with processing instructions in a laboratory manual. The tube types are serum, EDTA (plasma), and NaF/EDTA (plasma). Details of sample collection will be provided in the Central Laboratory Manual.

E. TIMING OF STUDY PROCEDURES

Subjects will provide written informed consent before any study-related procedures are performed. Subjects will sign informed consent on Visit 1E (Day 364) if they have not yet completed the main study, MRS-TU-2019.

The planned study assessments are presented in Section F Schedule of Assessments: ABPM Extension Study.

Visit 1E, Day 364 (± 3 days and 1 day prior to planned Visit 2E)

- The subject should arrive in a fasted state for the visit between 7 AM and 9 AM, and all subsequent visits should be at approximately the same time (± 60 mins).
- In addition, after the subject provides the signed informed consent form on Visit 1E, visit procedures include assessment for eligibility against the inclusion and exclusion criteria.
- AEs will be evaluated and recorded using non-leading questions and any changes in concomitant medication will be documented.
- The subject will undergo ABPM training and the ABPM recorder will be applied to the subject.
- Automated Self-Administered 24-hr Recall (ASA24) system **assigned breakfast meal should be given approximately 30 mins (± 5 mins) after ABPM cuff has been in place.**
- Dose of **study medication should be given approximately 30 mins (± 5 mins) after start of breakfast.**

End of Treatment/ D365/ Visit 2E, on Day 365 (±3 days MRS-TU-2019, +3 to +5 days / -3 days for MRS-TU-2019EXT)

Visit 2E will take place on Day 365 (±3 days) of completion of a subject's participation in the MRS-TU-2019, *however for subjects continuing in MRS-TU-2019EXT, the "+" window may be extended to +5 days if the 24-hr ABPM session requires repeating*, per Section C, ABPM Procedure.

Study procedures for MRS-TU-2019 EOT/ Day 365 visit are unchanged from Section 8.3.10, *except for those subjects participating in the MRS-TU-2019 EXT study, who will have the following additional assessment of ABPM data and adjustment to the vital signs procedure:*

- **Subject should arrive in a fasted** state for the visit, between 7 AM and 9 AM, and all subsequent visits should be at approximately the same time (± 60 mins).
- **Subject should not smoke within 30min of the start of the study visit, because in-clinic BP and Heart Rate are being assessed.**
- The subject will return for ABPM download and review.
  - If the 24-hr ABPM session download meets "pass" criteria (does not "fail"), proceed with all D365 / Visit 2E procedures including fasting labs.
  - If the 24-hr ABPM session download meets "fail" criteria, the subject will be requested to repeat the ABPM session within 2 days.
    - *In order to perform a repeat 24-hr ABPM assessment session, the D365 / V2E visit will need to be delayed (1 to 2 days later than planned).*
    - *To perform a repeat 24-hr assessment session, the application of ABPM recorder, meal time and dosing time should be the same as those for the original ABPM session (±60 mins).*
    - If the repeat 24-hr ABPM assessment "fails", the remainder of the visit assessments should proceed and the visit be completed. The subject may continue in the study.
  - Collect information about any unusually stressful activity or life events for the subject during the 24-hr ABPM collection period, such as:

    Did the subject experience any of the following during this 24-hour home BP monitoring period?
    - *Unusual activity?*
    - *Unusual diet?*
    - *Unusual stressful event?*

    Unusual events are described as those events that are unusual to the individual subject's activities or experiences of daily living.
- Vital signs (BP, heart rate, weight, and temperature) will be measured. The clinic BP will be measured in the non- dominant arm using a cuff and bladder appropriate to the subject's mid-arm circumference, according to AHA guidelines (*Hypertension*. 2005; 45:142- 161). The subject should be in the sitting position for at least 5 mins prior to the measurement and the arm should be supported at the heart level (mid-chest height). The BP should be obtained in triplicate, at least 1 min (+5min) apart in the sitting position.

- Providing ASA24 assigned breakfast is optional at this visit upon completion of fasting labs and vital signs.
- AEs will be evaluated and recorded using non-leading questions and any changes in concomitant medication will be documented.

Extension Study Pre-Treatment Period (Drug Washout Period)- For Continuing and Late Entry MRS-TU-2019 Subjects

Late Entry Subject to MRS-TU-2019EXT:

Subjects who already completed Day 365 of the main study MRS-TU-2019, prior to the start of MRS-TU-2019EXT, may provide informed consent at an unscheduled visit and enroll in the EXT study, bypassing the ABPM extension study Day 364-365 visit requirements.

- In general, these subjects are still required to begin the additional 8-weeks of washout visits required in MRS-TU-2019EXT (consent visit to V3E 4 weeks later, and to V7E 8-weeks later), prior to moving into the treatment phase. **However, exception may be made to the additional 8-week washout requirement for Late Entry Subjects under the following circumstance:**
  - At selected new enrollment centers, subjects who completed the main MRS-TU-2019 study ≥ 8 weeks prior and had not yet entered into MRS-TU-2019EXT, may be enrolled as a new enrollment subject, providing they meet all eligibility criteria specified for new enrollment subjects.

- *Any interim testosterone therapy between time of completion of MRS-TU-2019 and consent for MRS-TU-2019EXT, must be recorded in the electronic case report form.* As with other participating subjects, they must pass the ABPM evaluation at V7E/D1E to continue in the ABPM extension study.

ALL SUBJECTS: Continuing and Late Entry subjects who do not qualify as a new enrollment subject:

Visit 3E will take place 28 days (~4 weeks), Visit 4E will take place 42 days (~ 6 weeks) and **Visit 5E will take place 49 days (~7 weeks)** after the last dose of MRS-TU- 2019 or after date of consent for a late entry extension study subject. These visits all have a (+3 days) window.

- **Subjects should arrive in a fasted state** at clinic between 7 AM and 9 AM, and the visit should be at approximately the same time (± 60 mins) across all subsequent visits.
- **Subject should not smoke within 30min of the start of the study visit**, because in-clinic BP and Heart Rate are being assessed.

- Vital signs will be recorded (BP, heart rate, weight, and temperature). The clinic BP will be measured in the non-dominant arm using a cuff and bladder appropriate to the subject's mid-arm circumference, according to AHA guidelines (*Hypertension*. 2005; 45:142-161). The BP should be obtained in triplicate, at least 1 min (+5min) apart in the sitting position for at least 5 mins prior to the measurement and the arm should be supported at the heart level (mid-chest height).
- AEs will be evaluated and recorded using non-leading questions and any changes in concomitant medication will be documented.

Visit 6E will take place 55 days (+ 3d) after last dose of MRS-TU219, or after the date of consent for a late entry extension study subject (within 1 day prior to Visit 7E, Day 1E).

- The subject should **arrive in a fasted state** for the visit between 7 AM and 9 AM, and all subsequent visits should be at approximately the same time (± 60 mins).
- **Subject should not smoke within 30min of the start of the study visit**, because in-clinic BP and Heart Rate are being assessed.
- **Vital signs will be recorded** (BP, heart rate, weight, and temperature). The clinic BP will be measured in the non-dominant arm using a cuff and bladder appropriate to the subject's mid-arm circumference, according to AHA guidelines (*Hypertension*. 2005; 45:142-161). The BP should be obtained in triplicate, at least 1 min (+5min) apart. The subject should be in the sitting position for at least 5 mins prior.
  - **Any subject with an in-clinic, average BP > 140/90 at Visit 6E, must be withdrawn from further participation in MRS-TU-2019EXT ABPM Extension Study.**
- **ASA24 assigned breakfast meal should be given approximately 30 mins after arrival at clinic (+ 10 mins).**
- **AEs will be evaluated and recorded using non-leading questions and any changes in concomitant medication will be documented.**
- The ABPM recorder will be applied for the next 24 hours.

New Subject Enrollment Pre-treatment Visit Procedures:

For new subject enrollment at select centers, see 16.12.2 ABPM Extension Study Pre-Treatment Period: For Newly Enrolled Subjects (MRS-TU-2019 naïve).

Screening Visit 1(EXT)- (Day -21 to Day -11 from Visit 6E)

Screening Visit 1(EXT) should occur between 7 a.m. and 9 a.m. and not more than 21 days before Visit 6E.

After the subject provides the signed informed consent form, visit procedures include:

- Assess for eligibility against the inclusion and exclusion criteria.
- Collect full medical history and review concomitant medications.
- Record demographic data, such as race, ethnic origin, and date of birth.
- Draw a blood sample to test total serum T level.

After the procedures, subjects will be given a meal diary to take home to record three days of breakfasts and dinners before the next visit.

Screening Visit 2(EXT)- (Day -10 to Day -7)

Visit 2(EXT) will take place a minimum of 4 days and not more than 11 days after Screening Visit 1(EXT).

- Subjects should arrive at the clinic between 7 a.m. and 9 a.m., having fasted for at least 8 hours. Subjects should remain well hydrated during fasting and drink at least one glass of water (240 mL or 8 oz) prior to visit. Subjects will be contacted the previous day to remind them to fast before Visit 2EXT; no food or drink except water for 8 hrs.
- At the investigator's discretion, subjects may be re-screened using the Visit 2(EXT) procedures, or individual laboratory tests may be repeated.

Visit procedures include:

- Reassess eligibility against the inclusion and exclusion criteria.
- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.
- Record vital signs (BP, heart rate, weight, and temperature).
  - BP will be measured using a cuff appropriate to the subject's arm size, in a standardized manner, i.e., after the subject has rested in the sitting position for 5 minutes. The cuff used for each subject should be noted along with its size, and the same cuff used throughout the study for that subject. Blood pressure measurements will be measured in the non-dominant arm, with the arm extended and supported at mid-chest height.
  - BP should be duplicated within 5 minutes. If the difference in sBP and dBP measurements is > 10 mm Hg and > 5 mm Hg, respectively, a third BP measurement will be taken and results averaged.
  - **Patients with an in-clinic, average BP > 140/90 at Screening Visit 2 (EXT), are prohibited from enrolling in MRS-TU-2019EXT and further screening activities should be discontinued.**
- Perform an ECG.

- Record height.
- Collect samples for biochemistry (includes T sample), endocrinology, hematology (including glycosylated hemoglobin [HbA1c]), urinalysis, lipid panel, and PSA.
- Collect samples for hepatitis B surface antigen and hepatitis C antibody, with confirmatory testing, i.e., detectable serum HCV RNA); collect HIV antibody tests.
- Collect urine sample for drug screening (includes cocaine, narcotics, benzodiazepines, tetrahydrocannabinol, barbiturates, and amphetamines).
- Perform a full physical examination that must include administering an IPSS questionnaire, assessment for the presence of gynecomastia, and digital rectal examination.
- Collect subject meal diary and enter information into ASA24 system in the presence of the subject.

Following confirmation of eligibility at Screening Visit 1(EXT) and Screening Visit 2(EXT), newly enrolled subjects may proceed to Visit 6E **for ABPM training and cuff application visit, one day prior to Visit 7E/D1E.**

See Appendix Section 16.12.2, ABPM Extension Study Pre-Treatment Period: For Newly Enrolled Subjects (MRS-TU-2019 naïve).

Visit 6E for **newly enrolled subjects** will take place within 1 week (+3days) of Visit 2(EXT) confirming eligibility (within 1 day prior to Visit 7E, Day 1E),

- **The subject should arrive in a fasted state** for the visit between 7 AM and 9 AM, and all subsequent visits should be at approximately the same time (± 60 mins).
- **Subject should not smoke within 30min of the start of the study visit**, because in-clinic BP and Heart Rate are being assessed.
- **Vital signs will be recorded** (BP, heart rate, weight, and temperature). The clinic BP will be measured in the non-dominant arm using a cuff and bladder appropriate to the subject's mid-arm circumference, according to AHA guidelines (Hypertension. 2005; 45:142-161). The BP should be obtained in triplicate, at least 1 min (+5min) apart. The subject should be in the sitting position for at least 5 mins prior.
  - **Any subject with an in-clinic, average BP > 140/90 at Visit 6E must be withdrawn from further participation in MRS-TU-2019EXT ABPM Extension Study.**
- ASA24 assigned breakfast meal should be given approximately 30 mins after arrival at clinic (+10 mins).

- AEs will be evaluated and recorded using non-leading questions and any changes in concomitant medication will be documented.
- The ABPM recorder will be applied for the next 24 hours.

TREATMENT PERIOD- All Subjects

Visit 7E, Day 1E will take place 56 days (+3 to +5 days) after last dose of MRS-TU2019 or after the date of consent for a late entry extension study subject, or within 11 days (+3 to +5 days) after Screening Visit 2(EXT) for a newly enrolled subject.

The visit window should be within +3 days, unless the 24-hr ABPM session in Visit 6E needs to be repeated per Section C: ABPM Procedure, in which case the "+" window may be extended to +5 days.

- **Subjects should arrive in a fasted state** at the clinic between 7 AM and 9 AM, and the visit should be at approximately the same time (± 60 mins) across all subsequent visits.
- The subject will return for ABPM download and review.
  - If the 24-hr ABPM session download meets **"pass"** criteria (not "fail"), proceed with all Visit 7E / Day1E procedures including fasting labs.
  - If the 24-hr ABPM session download meets **"fail"** criteria, the subject will be requested to repeat the 24-hr ABPM session within 2days.
    - *In order to perform a repeat 24-hr ABPM assessment session, then the* Visit 7E / Day1E *visit will need to be delayed (1 to 2 days later than planned).*
    - *To perform a repeat 24-hr assessment session, application of ABPM recorder, meal time and dosing time should be the same as those for the original ABPM session (±60 mins).*
    - **If both the original and repeat assessments meet "fail" criteria at V7E/ D1E, the subject must be withdrawn from further participation in the extension study.**
- Collect information about any unusually stressful activity or life events for the subject during the 24-hr ABPM collection period, such as:

  Did the subject experience any of the following during this 24-hour home BP monitoring period?
  - *Unusual activity?*
  - *Unusual diet?*
  - *Unusual stressful event?*

  Unusual events are described as those events that are unusual to the individual subject's activities or experiences of daily living.

- AEs will be evaluated and recorded using non-leading questions and any changes in concomitant medication will be documented.
- A full physical examination will be performed that must include an assessment for the presence of gynecomastia, and digital rectal examination.
  - **For newly enrolled subjects having had a **normal** full physical exam at V2(EXT), the full exam is not required to be repeated again at V7E, unless there is clinical reason to do so.*
- Collect pre-dose samples in a fasting state for biochemistry, endocrinology, hematology (to include HbA1c), lipid panel, and PSA.
- Collect pre-dose blood samples for serum T and dihydrotestosterone (DHT), estradiol (E2), plasma T and DHT (NaF/EDTA tube), plasma T and DHT (EDTA tube).
- Breakfast: Providing ASA24-assigned *breakfast **is optional** after fasting labs.*
- Dispense study medication (SOV2012-F1).
  - If optional breakfast meal was provided, dose in clinic 30min after start of meal.
  - If optional breakfast was not provided, instruct subject to dose 30min after the start of his morning meal.

Visit 8E, Day 14E (±3 days)

- **Subjects should arrive in a fasted state,** at the clinic between 7 AM and 9 AM, and the visit should be at approximately the same time (± 60 mins) across all subsequent visits.
- **Subject should not smoke within 30min of the start of the study visit**, because in-clinic BP and Heart Rate are being assessed.

  Vital signs will be recorded (BP, heart rate, weight, and temperature). The clinic BP will be measured in the non-dominant arm using a cuff and bladder appropriate to the subject's mid-arm circumference, according to AHA guidelines (*Hypertension*. 2005; 45:142-161). The BP should be obtained in triplicate, at least 1 min (+5min) apart. The subject should be in the sitting position for at least 5 mins prior to the measurement and the arm should be supported at the heart level (mid- chest height).
- AEs will be evaluated and recorded using non-leading questions and any changes in concomitant medication will be documented.
- Record symptom-directed physical examination.
- Pharmacokinetic (PK) samples are collected **pre-morning dose** and 1.5, 3, 4, 5, and 6 hours **after AM dose** of SOV2012-F1 (±5 mins for all timepoints). PK samples include plasma T and DHT.

- Serum T and DHT sample collected **pre-morning dose** and 1.5,3,4,5 and 6 hours **after AM dose** of SOV2012-F1 (±5 mins for all timepoints).
- Dosing and meals (See MRS-TU-2019 Protocol Section 7.1.1, Diet):
  - Breakfast meal must be based on subjects' ASA24 records.
  - **ASA Breakfast should be given after pre-dose lab is drawn**. Record meals, meal fat type (low, normal or high fat), and the percentage of meal consumed (0, 25%, 50%, 75%, 100%).
  - **Study medication will be administered 30 (±5) mins after the start of breakfast meal.**
  - Provide normal fat lunch meal of choice, or patient may bring in lunch of choice (4 hours after morning dose).

Visit 9E, Day 28E (±3 days)

- Subjects should arrive at the clinic between 7 AM and 9 AM, and the visit should be at approximately the same time across all subsequent visits (± 60 mins).
- AEs will be evaluated and recorded using non-leading questions visit and any changes in concomitant medication will be documented.
- Record symptom-directed physical examination.
- Perform a study medication accountability check for remaining study drug
- Dose adjustments, if needed, will be made.
- Dispense study medication based on dose for the next study interval, including any dose adjustment.

Visit 10E, Day 42E (±3 days)

- **Subjects should arrive in a fasted stated,** at the clinic between 7 AM and 9 AM, and the visit should be at approximately the same time across all subsequent visits (± 60 mins).
- **Subject should not smoke within 30min of the start of the study visit**, because in-clinic BP and Heart Rate are being assessed.
- **The vital signs will be recorded** (BP, heart rate, weight, and temperature). The clinic BP will be measured in the non-dominant arm using a cuff and bladder appropriate to the subject's mid-arm circumference, according to AHA guidelines (*Hypertension*. 2005; 45:142-161). The subject should be sitting for at least 5 mins prior to measuring BP, and the arm should be extended and supported at the level of the heart (mid-chest height). The BP

should be obtained in triplicate, 1 min (+5min) apart in the sitting position with the arm supported at the heart level (mid-chest height).

- AEs will be evaluated and recorded using non-leading questions and any changes in concomitant medication will be documented.
- Record symptom-directed physical examination.
- PK samples are collected **pre-morning dose** and **1.5, 3, 4, 5, and 6 hours after AM dose** of SOV2012-F1 (±5 min for all timepoints). PK samples include plasma T and DHT.
- Serum T and DHT sample collected **pre-morning dose** and 1.5,3,4,5 and 6 hours **after AM dose** of SOV2012-F1 (±5 mins for all timepoints).
- Dosing and meals (refer to MRS-TU-2019 Protocol Section 7.1.1, for dietary details which are unchanged):
  - Breakfast meal must be based on subjects' ASA24 records.
  - ASA **Breakfast should be given after pre-dose lab is drawn**. Record meals, meal fat type (low, normal or high fat), and the percentage of meal consumed (0, 25%, 50%, 75%, 100%).
  - **Study medication will be administered 30 (±5) mins after the start of breakfast meal.**
  - Provide normal fat lunch meal of choice, or patient may bring in lunch of choice (4 hours after morning dose).

Visit 11E, Day 56E (±3 days)

- **Subjects should arrive at the clinic between 7 AM and 9 AM,** and the visit should be at approximately the same time across all subsequent visits (± 60 mins).
- AEs will be evaluated and recorded using non-leading questions and any changes in concomitant medication will be documented.
- Record symptom-directed physical examination.
- Perform a study medication accountability check for any remaining study drug.
- Dose adjustments, if needed, will be made.
- Dispense study medication based on dose for the next study interval, including any dose adjustment.

Visit 12E / Day 90E (±3 days)

- **Subjects should arrive in a fasted state,** at the clinic between 7 AM and 9 AM, and the visit should be at approximately the same time across all subsequent visits (± 60 mins).
- **Subject should not smoke within 30min of the start of the study visit**, because in-clinic BP and Heart Rate are being assessed.
- The visit will be a 24-hour confinement visit.
- The vital signs will be recorded (BP, heart rate, weight, and temperature). The clinic BP will be measured in the non-dominant arm using a cuff and bladder appropriate to the subject's mid-arm circumference, according to AHA guidelines (*Hypertension*. 2005; 45:142-161). The subject should be sitting for at least 5 mins prior to measuring BP, and the arm should be extended and supported at the level of the heart (mid-chest height). The BP should be obtained in triplicate, 1 min (+5min) apart in the sitting position with the arm supported at the heart level (mid-chest height).
- AEs will be evaluated and recorded using non-leading questions and any changes in concomitant medication will be documented.
- Record symptom-directed physical examination.
- Collect **pre-dose samples** for biochemistry, endocrinology, hematology (to include HbA1c), lipid panel, and PSA.
- Collect PK samples **pre-morning dose** and 1.5, 3, 4, 5, 6, 8, 12, 13.5, 15, 16, 17, 18, 20, and 24 hours **after AM dose** of SOV2012-F1 (±5 mins for all timepoints). PK plasma samples include E2, testosterone undecanoate (TU) and dihydrotestosterone undecanoate (DHTU); T and DHT.
- ***24-hr Serum T Substudy Participants:** Subjects enrolled in the Serum T substudy should have Serum T samples drawn at all PK **timepoints: pre-morning dose** and 1.5, 3, 4, 5, 6, 8, 12, 13.5, 15, 16, 17, 18, 20, and 24 hours **after AM dose**
- Dosing and meals (See MRS-TU-2019 Protocol Section 7.1.1, Diet, for additional detail which is unchanged):
  - Provide breakfast and dinner meals **based on subjects' ASA24 records.**
  - **ASA Breakfast is provided after fasting and pre-dose labs. Study Medication AM dose is provided 30 (±5) mins after start of AM meal.**
  - Provide normal fat lunch meal selection of choice, or subject may bring in own lunch; to be eaten 4 hours after AM dosing.

- **ASA Dinner is provided 12 hours after AM meal. Study medication PM dose is administered 30 (±5) mins after the start of the dinner meals.**
- For both ASA breakfast and dinner meals, record meals, meal fat type (low, normal or high fat), and the percentage of meal consumed (0, 25%, 50%, 75%, 100%).

- Perform a study medication accountability check for any remaining study drug.
- Dispense study medication.

Visit 13E, Day 119E (±3 days, but within 1 day of V14E)

- **The subject should arrive in a fasted state** for the visit between 7 AM and 9 AM, and all subsequent visits should be at approximately the same time (±60 mins).
- **Subject should not smoke within 30min of the start of the study visit**, because in-clinic BP and Heart Rate are being assessed.
- **The vital signs will be recorded** (BP, heart rate, weight, and temperature). The clinic BP will be measured in the non-dominant arm using a cuff and bladder appropriate to the subject's mid-arm circumference, according to AHA guidelines (*Hypertension*. 2005; 45:142-161). The subject should be sitting for at least 5 mins prior to measuring BP, and the arm should be extended and supported at the level of the heart (mid-chest height). The BP should be obtained in triplicate, 1 min (+5min) apart in the sitting position with the arm supported at the heart level (mid-chest height).
- AEs will be evaluated and recorded using non-leading questions, and any changes in concomitant medication will be documented.
- Record symptom-directed physical examination.
- The ABP recorder will be applied on the subject for the next 24 hours.
- ASA24 **assigned breakfast meal should be given approximately 30 min after arrival at clinic** (+ 10 min).
- Dose of **study medication should be given approximately 30 mins after start of breakfast** (60 [± 5 mins] after start of ABPM).

Visit 14E, Day 120E ((±3days).

- **Subjects should arrive in a fasted state** at the clinic between 7 AM and 9 AM, and the visit should be at approximately the same time (± 60 mins) across all subsequent visits.
- The subject will return for ABPM download and review.

- If the download is successful (does not meet the specified fail criteria); the rest of the visit procedures may proceed.
- If the 24-hr ABPM session download meets "fail" criteria, the subject will be requested to repeat the 24-hr ABPM session within 2 days.
- *To perform a repeat 24-hr assessment session, application of ABPM recorder, meal time and dosing time should be the same as those for the original ABPM session (±60 mins).*
  - A repeat 24-hr assessment may be attempted a second time at the discretion of the Investigator. As a reminder, if a second repeat is scheduled the subject must fast the night before.
- If both the original ABPM data download and the repeat ABPM data download meet "fail" criteria, the rest of the visit procedures should be completed. The subject may continue in the extension study.

- Collect information about any unusually stressful activity or life events for the subject during the 24-hr ABPM collection period, such as:

  Did the subject experience any of the following during this 24-hour home BP monitoring period?
  - *Unusual activity?*
  - *Unusual diet?*
  - *Unusual stressful event?*

  Unusual events are described as those events that are unusual to the individual subject's activities or experiences of daily living.
- AEs will be evaluated and recorded using non-leading questions and any changes in concomitant medication will be documented.
- Record symptom-directed physical examination.
- Perform a study medication accountability check for any remaining study drug.
- Dispense study medication.

Visit 15E, Day 179E (±3 days, but within 1 day of V16E)

- **The subject should arrive in a fasted state** for the visit between 7 AM and 9 AM, and all subsequent visits should be at approximately the same time (± 60 mins).
- **Subject should not smoke within 30min of the start of the study visit**, because in-clinic BP and Heart Rate are being assessed.
- **The vital signs will be recorded** (BP, heart rate, weight, and temperature). The clinic BP will be measured in the non-dominant arm using a cuff and bladder appropriate to the subject's mid-arm circumference, according to

AHA guidelines (*Hypertension*. 2005; 45:142-161). The subject should be sitting for at least 5 mins prior to measuring BP, and the arm should be extended and supported at the level of the heart (mid-chest height). The BP should be obtained in triplicate, 1 min (+5min) apart in the sitting position with the arm supported at the heart level (mid-chest height).

- AEs will be evaluated and recorded using non-leading questions, and any changes in concomitant medication will be documented.
- Record symptom-directed physical examination.
- The ABP recorder will be applied on the subject for the next 24 hours.
- **ASA24 assigned breakfast meal should be given approximately 30 min after arrival** at clinic (+ 10 min).
- **Dose of study medication should be given approximately 30 mins after start of breakfast** (60 [± 5 mins] after start of ABPM).

Visit 16E/ EOT, Day 180E (±3days).

- **Subjects should arrive in a fasted state** at the clinic between 7 AM and 9 AM, and the visit should be at approximately the same time (± 60 mins) across all subsequent visits.
- The subject will return for ABPM download and review.
  - If the download meets "pass" criteria (does not meet fail criteria); *the rest of the visit procedures may proceed.*
  - If the 24-hr ABPM session download meets "fail" criteria, the subject will be requested to repeat the 24-hr ABPM session within 2 days.
  - *To perform a repeat 24-hr assessment session, application of ABPM recorder, meal time and dosing time should be the same as those for the original ABPM session (±60 mins).*
    - A repeat 24-hr assessment **may be attempted a second time** at the discretion of the Investigator. As a reminder, if a second repeat is scheduled the subject must fast the night before.
  - If both the original ABPM data download and the repeat ABPM data download meet "fail" criteria, the rest of the visit procedures should be completed.

- Collect information about any unusually stressful activity or life events for the subject during the 24-hr ABPM collection period, such as:
  Did the subject experience any of the following during this 24-hour home BP monitoring period?
  - *Unusual activity?*
  - *Unusual diet?*
  - *Unusual stressful event?*

  Unusual events are described as those events that are unusual to the individual subject's activities or experiences of daily living.

- AEs will be evaluated and recorded using non-leading questions and any changes in concomitant medication will be documented.
- Perform a full physical examination that must include an assessment for the presence of gynecomastia, and digital rectal examination.
- **Collect pre-dose samples** for biochemistry, endocrinology, hematology (to include HbA1c), lipid panel, and PSA.

Early Withdrawal Visit E

- **Subjects should arrive in a fasted state** at the clinic between 7 AM and 9 AM, and the visit should be at approximately the same time across all subsequent visits (± 60 mins).
- **Subject should not smoke within 30min of the start of the study visit**, because in-clinic BP and Heart Rate are being assessed.
- **The vital signs will be recorded** (BP, heart rate, weight, and temperature). The clinic BP will be measured in the non-dominant arm using a cuff and bladder appropriate to the subject's mid-arm circumference, according to AHA guidelines (*Hypertension*. 2005; 45:142-161). The subject should be sitting for at least 5 mins prior to measuring BP, and the arm should be extended and supported at the level of the heart (mid-chest height). The BP should be obtained in triplicate, 1 min (+5min) apart in the sitting position with the arm supported at the heart level (mid-chest height).
- Record full physical examination.
- AEs will be evaluated and recorded using non-leading questions since the previous visit and any changes in concomitant medication will be documented.
- **Collect fasted samples** for biochemistry, endocrinology, hematology (excluding HbA1c), and PSA.
- Perform an accountability check for any remaining study drug.

Post Treatment Period

Follow-up Safety Phone Call (7 days, ±3 days) after last dose of SOV2012-F1 in MRS-TU-2019EXT.

- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.

F. SCHEDULE OF ASSESSMENTS: ABPM EXTENSION STUDY

16.12.1. EOT MAIN STUDY AND ABPM EXTENSION PRE-TREATMENT PERIOD- for MRS-TU-2019 Continuing and Late Entry Subjects (who do not qualify as a new enrollment subject)

	MRS-TU-2019 EOT Main Study and MRS-TU-2019EXT Study Start			**MRS-TU-2019EXT ABPM Extension Study PRE-TREATMENT WASH-OUT PERIOD**				
	Visit 1E[a] MRS-TU-2019EXT Day 364 (±3d); within1day prior to V2E[a])	EOT/ D365 or Early Withdraw ((±3d)[b] **and Visit 2E**[a] **MRS-TU-2019EXT** (+3d to +5d/-3d)[b]	Follow Up Phone Call (14days (±3d) After Last Dose	**ABPM EXT Late Entry Consent**[s] (-28d +3) From Visit 3E)	**Visit 3E**[s] 28 days/4 weeks (+3d) After Last Dose MRS- **Or** EXT Consent	**Visit 4E** 42 days/ 6 weeks (+3d) After Last dose MRS-TU-2019 **Or** EXT Consent	**Visit 5E** 49 days/7 weeks (+3d) After Last Dose MRS-TU-2019 **Or** EXT Consent	**Visit 6E** 55 days (+3d) After Last Dose MRS-TU-2019 **Or** EXT Consent (within 1d prior 7E/ D1E)
FASTING VISIT	X	X			X	X	X	X
Informed consent -E	X[s]			X[s]				
Inclusion/exclusion criteria	X			X[s]				
Concomitant medications	X	X	X	X	X	X	X	X
Physical examination		X (req)						
Vital signs[d]		X			X	X	X	X
Biochemistry[e]		X						
Endocrinology[f]		X						
Hematology[g]		X						
Fasting insulin		X[h]						
Lipid panel (TC, LDL, HDL, TGs)		X						
PSA		X						
ACTH stimulation testing		X[i]						
Perform accountability check[p]		X						

Table continues on next page.

	MRS-TU-2019 EOT Main Study and MRS-TU-2019EXT Study Start			MRS-TU-2019EXT ABPM Extension Study PRE-TREATMENT WASH-OUT PERIOD				
	Visit 1E[a] MRS-TU-2019EXT Day 364 (±3d); within1day prior to V2E[a])	**EOT/ D365 (±3d)**[b] **(or** Early Withdraw Visit) MRS-TU-2019 **and Visit 2E**[a] **MRS-TU-2019EXT** (+3d to +5d/-3d)[b]	**Follow Up Phone Call** (14days (±3d) After Last Dose	**ABPM EXT Late Entry Consent**[s] (-28d +3) From Visit 3E)	**Visit 3E**[s] 28 days/4 Weeks (+3d) After Last Dose MRS-2019 **Or** EXT Consent	**Visit 4E** 42 days/ 6 weeks (+3d) After Last Dose MRS-TU-2019 **Or** EXT Consent	**Visit 5E** 49 days/7 weeks (+3d) After Last Dose MRS-TU-2019 **Or** EXT Consent	**Visit 6E** 55 days (+ 3d) After Last Dose MRS-TU-2019, **or** EXT Consent (within 1d prior to Visit 7E/ D1E)
Single-draw PK, SOV2012-F1 group: plasma T, DHT		X[l] (3-5 hr post)						
Single-draw PK, AndroGel group: serum T, DHT		X						
I-PSS		X						
PDQ collect		X						
IIEF		X						
SF-36		X						
ASA24 Breakfast[n] (On dosing days, start Breakfast 30 min prior to dose)	X[n] (req)	X[n] (opt)						X[n] (req)
Adverse event reporting	X	X	X	X	X	X	X	X
ABPM Subject Training and Demo[a] for MRS-TU- 2019EXT	X[a s]							X[s]
Distribute ABPM Unit for MRS-TU-2019EXT	X[a]							X[s]
Collect ABPM Data for MRS- TU-2019EXT		X[r]						

Table continues on next page.

16.12.2. ABPM Extension Study Pre-Treatment Period: For Newly Enrolled Subjects (MRS-TU-2019 naïve or Late Entry subjects who qualify for new enrollment) [t]

	MRS-TU-2019EXT NEW Subject Consent and Screening Visit 1-2(EXT) [t]		MRS-TU-2019EXT ABPM Extension Study PRE-TREATMENT Period
	NEW Subject Screening Visit 1(EXT) [t] (Day -21 to -11 from V6E)	NEW Subject Screening Visit 2(EXT) [t] (Day -10 to -7 from V6E)	Visit 6E (Within 10days of Visit 2(EXT) (and 1d prior to Visit 7E/ D1E)
FASTING VISIT	X	X	X
Informed consent -E	X		
Inclusion/exclusion criteria for MRS-TU-2019 and MRS-TU-2019EXT		X	
Demographic data	X		
Medical history	X		
Concomitant medications	X	X	
Adverse Event Reporting	X	X	X
Physical examination		X	
Height		X	
Vital signs[d]		X	X
ECG		X	
Urinalysis[e]		X	
Urine drug screen[f]		X	
HIV, hepatitis screens		X	
Biochemistry[g]		X	
Endocrinology[h]		X	
Hematology[i]		X	
Total testosterone, serum	X[j]	X[j]	
Lipid panel (TC, LDL, HDL, TGs)		X[z]	
PSA		X	
Distribute and collect ASA 3day Breakfast and Dinner Food Diary for entry into ASA 24-hr system [t]	X.[t]	X[t]	
ABPM Subject Training and Demo[a] for MRS-TU- 2019EXT			X
Distribute ABPM Unit for MRS-TU-2019EXT			X

16.12.3. ABPM Extension Study Treatment Period for All Subjects

	MRS-TU-2019EXT ABPM Extension TREATMENT PERIOD											Post-Treatment
	Visit 7E Day1E (56 days +3d to 5d) After Last Dose MRS-TU-2019, Or EXT Consent Date [s]	**Visit 8E** Day 14E (±3d)	**Visit 9E** Day 28E (±3d)	**Visit10E** Day 42E (±3d)	**Visit 11E** Day 56E (±3d)	**Visit 12E** Day 90E (±3d)	**Visit 13E** Day 119E (±3d) (within 1d Prior to Visit 14E)	**Visit 14E** Day 120E (±3d)	**Visit 15E** Day 179E (±3d) (within 1d prior to Visit 16E)	**Visit 16E** EOT Day 180E (±3d)	**Early WD Visit E**	**Safety Follow-up Call E** (7 days (±3d) After Last Dose MRS-TU-2019EXT
FASTING VISIT	X	X		X		X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Reporting	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X (req)	X (SD)	X (SD)	X (SD)	X (SD)	X (SD	X (SD)	X (SD)	X (SD)	X (req)	X (req)	
Vital signs[d]		X		X		X	X		X		X	
Biochemistry[e]	X					X				X	X	
Endocrinology[f]	X					X				X	X	
Hematology[g]	X					X				X	X	
PSA	X					X				X	X	
Lipid panel (TC, LDL, HDL,TGs)	X					X				X		
Total Serum T and DHT	X(pre-dose)	X[j]		X[j]								
Plasma T and DHT (in NaF-EDTA, EDTA)	X (pre-dose)											
6-hour PK sampling, plasma T, DHT (NaF EDTA and EDTA)[j]		X		X								
24-hour PK sampling, plasma T, DHT (NaF EDTA and EDTA)[k]						X						
24-hour PK sampling, plasma (NaF EDTA) TU, DHTU[k]						X						

Table continues on next page.

	MRS-TU-2019EXT ABPM Extension TREATMENT PERIOD											Post-Treatment
	Visit 7E Day1E (56 days +3d to 5d) After Last Dose MRS-TU-2019, Or EXT Consent Date	**Visit 8E** Day 14E (±3d)	**Visit 9E** Day 28E (±3d)	**Visit 10E** Day 42E (±3d)	**Visit 11E** Day 56E (±3d)	**Visit 12E** Day 90E (±3d)	**Visit 13E** Day 119E (±3d) within 1d prior to to V14E	**Visit 14E** Day 120E (±3d)	**Visit 15E** Day 179E (±3d) within 1d prior to V16E	**Visit 16E** EOT Day 180E (±3d)	**Early WD** Visit E	**Safety Follow-up Phone Call E** 7 days (±3d) After Last Dose MRS- TU-2019
24-hr Serum T Substudy Subjects [u]						X [u]						
E2 (Single or 24-hour PK), SOV2012-F1[l]	X (pre- dose)					X						
Dose adjustments[m]			X		X							
ASA24 Breakfast, 30 min prior to dose[n]	X[n] (opt)						X[n] (req)		X[n] (req)			
ASA24 Breakfast 30 mins prior to dose, and Normal Lunch served[n] (4-hrs post dose)		X[n]		X[n]								
All meals served (Breakfast and Dinner per ASA24-assigned meal; Normal Lunch)[o]						X						
Dispense study medications	X		X		X	X		X				
Perform accountability check[p]			X		X	X		X		X	X	
Distribute ABPM Unit for MRS-TU- 2019EXT							X		X			
Collect ABPM Data for MRS-TU-2019EXT	X[r]							X[r]		X[r]		

Abbreviations: ABPM = ambulatory blood pressure monitoring ACTH = adrenocorticotropic hormone; ALT = alanine aminotransferase; ASA24 = Automated Self-Administered 24-Hour Recall system; AST = aspartate aminotransferase; ALP = alkaline phosphatase; BP = blood pressure; BUN = blood urea nitrogen; DHT = dihydrotestosterone; DHTU = dihydrotestosterone undecanoate; E2 = estradiol; eGFR = estimated glomerular filtration rate; EOT = end of treatment; FSH = follicle-stimulating hormone; HbA1c = glycosylated hemoglobin; HDL = high-density lipoproteins; IIEF = International Index of Erectile Function; I-PSS = International Prostate Symptom Score; LDH = lactate dehydrogenase; LDL = low-density lipoproteins; LH = luteinizing hormone; opt = optional; N/A = not applicable; PDQ = Psychosexual Daily Questionnaire; PK = pharmacokinetic; PSA = prostate-specific antigen; rec = required; SD = symptom-directed; SF-36 =

Short Form Survey; SHBG= sex hormone-binding globulin; T = testosterone; TC = total cholesterol; TGs = triglycerides; TSH = thyroid-stimulating hormone; TU = testosterone undecanoate; WBC = white blood cells; WD = withdrawal

a. Visit applies to the MRS-TU-2019EXT ABPM Extension subjects only.
b. All subjects come to the clinic having fasted for at least 8 hours. Subjects should remain well hydrated during fasting and drink at least one glass of water (240 mL or 8 oz) prior to visit. Subjects should have completed 7-day PDQ questionnaire and all lab results should be available.
c. Full physical examination must include assessment for the presence of gynecomastia, and digital rectal examination at End of Treatment in main study (EOT/Day 365), Visit 7E (Day 1E), and V16E (Day180) and at early withdrawal visit. At all other visits, subjects should undergo a symptom-directed (SD) physical examination
d. Vital signs include BP, heart rate, temperature, and weight. Blood pressure will be measured using a cuff appropriate to the subject's arm size, in a standardized manner, i.e., after the subject has rested in the sitting position for at least 5 minutes. Beginning with Visit Day 365/V2E, BP at all visits during the MRS-TU-2019EXT, BP should be obtained after the subject is seated for at least 5 mins prior to measuring BP, and the arm should be extended and supported at the level of the heart (mid-chest height). The BP should be obtained in triplicate, 1 min (+5min) apart in the sitting position with the arm supported at the heart level (mid-chest height). At the Day 365/V2E, BP should be measured in the dominant arm at all visits). **Any subject with an in-clinic, average BP > 140/90 at Visit 6E, should be withdrawn from further MRS-TU-2019EXT participation.**
e. Biochemistry includes AST, ALP, ALT, total bilirubin, creatinine, BUN, eGFR, LDH, glucose, total protein, albumin, sodium, potassium, calcium, and phosphorus. At Visit 7/Day 1E the labs will be obtained pre-dose and fasted.
f. Endocrinology consists of LH, FSH, SHBG, and TSH.
g. Hematology includes hemoglobin, hematocrit, WBC, platelets, and HbA1c (except at Early Withdraw when no HbA1c will be analyzed).
h. For early withdrawal subjects, fasting insulin is not collected.
i. ACTH stimulation testing is performed as a substudy in MRS-TU-2019 main study only (45 subjects enrolled for 30 completers, 2:1 ratio between SOV2012-F1 and AndroGel™.)
j. Visit 8E (Day 14E) and 10E (Day 42E) collect PK only at these timepoints as it is not an overnight visit in this extension: PK samples are collected pre-morning dose and 1.5, 3, 4, 5, and 6 hours, after AM dose of SOV2012-F1 (±5 mins for all timepoints). PK samples include plasma T and DHT, and serum T and DHT. The initial dose is administered 30 (±5) mins after the start of breakfast meal.
k. Visit12E (Day 90E) is a 24-hr confinement and will include the same timepoints as SOV2012-F1 confinement visit at 90 days in MRS-TU-2019: PK samples are collected pre-morning dose and 1.5, 3, 4, 5, 6, 8, 12, 13.5, 15, 16, 17, 18, 20, and 24 hours after AM dose of SOV2012-F1 (±5 mins for all timepoints). PK samples include plasma T and DHT, plasma TU and DHTU. The initial and 12-hr doses are administered 30 (±5) mins after the start of breakfast and dinner meals.
l. PK samples on these days should be **drawn after the morning dose of SOV2012-F1 between <u>3-5 hours (+10min) post-morning dose</u>**. PK samples include plasma T and DHT. For early withdrawal subjects, no PK sample is collected.
m. Dose adjustments, if needed, will be made on these days.
n. Providing breakfast is optional after fasting labs at EOT / Day 365 / Visit 2E, and on Visit 7E / Day 1E.
Breakfast (MRS-TU-2019 ASA-assigned meal type) is required on Visit 1E, 6E, 13E and 15E, after applying ABPM cuff.
Breakfast (ASA24-assigned) and lunch (normal fat or lunch of choice) are to be provided on Visit 8E and Visit 10E. Lunch should be given approximately 4 hours after morning dose.
o. Provide all 3 meals. Breakfast and dinner should be based on subjects' ASA24 records (all lunches are to be chosen from normal fat menu or subject may have selection of choice) and record meals, meal fat type, and the percentage of meal consumed (0, 25%, 50%, 75%, 100%). Lunch should be given approximately 4 hours after dose.
p. Perform an accountability check for any remaining study drug.
q. If both the initial and repeat 24-hr ABPM assessment session at V7E/ Day 1E, the subject should be withdrawn from MRS-TU-2019EXT study.
r. If ABPM data download quality equals "fail" status, subject may repeat the ABPM evaluation within 2 days. The subject can be sent home with the ABPM cuff for another 24-hr period of collection and return at the completion of the repeat 24-hr recording session, in which case the V2E / D365 or V7E / D1E visit will be delayed (to occur up to 2 days later than planned, using the longer "+" window). At Visit 14E (day 120) and Visit 16E (Day 180), a repeat 24-hr assessment **may be attempted a second time** at the discretion of the Investigator. As a reminder, if a second repeat is scheduled the subject must fast the night before

s. **LATE ENTRY MRS-TU-2019 EXT SUBJECTS who do not qualify for new enrollment:** Subjects who already completed D365 of the main study MRS-TU-2019 prior to the start of MRS-TU-2019EXT, ,may provide informed consent and enter the EXT study after the D364-365 requirements These subjects will still be required to begin an additional 8-week washout period from the time of consenting Visit 3E should occur 28days (4weeks) from time of consent. .. **ABPM SUBJECT TRAINING SHOULD OCCUR IN THIS INSTANCE, ON V6E.**

t **New Subject Enrollment for EXT** (naïve to MRS-TU-2019): ASA Food Diary should be provided to new subjects at Screening Visit 1(EXT). Diary completion for 3 days of typical breakfast and dinner meals should be completed by Screening Visit 2(EXT) and entered into the ASA-24hr system in order to enter diet data into eCRF to obtain diet assignment information needed for meal at V6E. ***Subjects who would otherwise be considered Late Entry Subjects from the main study MRS-TU-2019 and completed the main study >8 weeks before start of MRS-TU-2019EXT, may be considered for new subject screening*** *and enter the MRS-TU-2019EXT by way of the new enrollment subject pathway.*

u **24-hr Serum T Substudy subjects** should have serum T drawn at all 24hr PK timepoints at V12E/D90E: pre-morning dose and 1.5, 3, 4, 5, 6, 8, 12, 13.5, 15, 16, 17, 18, 20, and 24 hours after AM dose

G. OVERALL DESIGN

Number of Subjects

Up to approximately 170 completed MRS-TU-2019 subjects will be consented to the MRS- TU- 2019EXT Study to undergo 8 weeks or more of study medication or interim testosterone replacement washout, followed by a total of 180 days of treatment with SOV2012-F1. Subjects will dose-titrate to their final dose over the first 28-56 days of the treatment period. The MRS-TU-2019 EXT Extension Study will include three to four 24-hour ABPM assessment sessions, depending on at which timepoint the subject enters the study (directly from MRS-TU-2019 or as a Late Entry Subject to MRS-TU-2019EXT or as a newly enrolled MRS_TU-2019- naïve subject).
Approximately 135 of the approximately 170 consented subjects (80%) are targeted to complete 120days of the 180-day treatment period, including at minimum, the baseline V7E/Day 1E and the 4-month Visit 14E/ Day 120E required 24-hr ABPM assessment sessions in MRS-TU-2019EXT.

Inclusion/Exclusion Criteria*

Inclusion criteria:

1. Completion of MRS-TU-2019 Day 365/ End of Treatment

Exclusion criteria:

1. Upper arm circumference > 45 cm.
2. Long distance driving or planned driving trip (> 60 mins duration where the subject is doing the driving) during period of wearing ABPM cuff.
3. Expected / known forthcoming change to antihypertensive medication(s) during the MRS-TU-2019 EXT extension study.
4. Cardiac arrhythmias that, in the opinion of the investigator, interfere with the ability of the ABPM recorder to obtain reliable measurements.
5. Use of T implantable pellets since completion of Day 365/EOT visit in MRS-TU- 2019.

Exception to this MRS-TU-2019EXT** eligibility criteria**

***New Subject Enrollment into MRS-TU-2019EXT**: Enrollment of patients naïve to MRS-TU-2019 will be permitted at a few sites in order to maximize enrollment for MRS-TU-2019EXT, provided that those patients meet both the main study and extension study eligibility criteria. These subjects **would be required to consent and then complete screening assessments of the Screening Visit 1(EXT) and Screening Visit 2(EXT), consistent with the main protocol, prior to being enrolled into MRS-TU-2019EXT. See 16.12.2 Schedule of Assessments-** ABPM Extension Study Pre-Treatment Period: For Newly Enrolled Subjects (MRS-TU-2019 naïve, or main study Late Entry subjects who have been off study for an extended period of 8 weeks or more and qualify for new enrollment.).

Treatment During Extension Study, MRS-TU-2019EXT

During the MRS-TU-2019EXT study period, all subjects will be washed out from their originally assigned MRS-TU-2019 study medication or any interim testosterone replacement for an 8-week period. At the completion of that washout, all subjects will receive SOV2012- F1, starting at a total daily dose of 400 mg (200 mg with the breakfast meal and 200 mg with the dinner meal) and titrated, if needed, according to the dose-titration algorithm established for the MRS-TU-2019EXT Extension Study protocol.

Dietary guidance and meal content are unchanged from Section 7.1.1 of MRS-TU-2019 protocol.

Extension Study Duration

The duration of the Extension Study (MRS-TU-2019EXT) is approximately 8.5 months (195 days), including a minimum 8-week study medication (or prior testosterone replacement) washout, followed by a total of 180 days of lower starting dose oral SOV2012-F1 treatment, and a 1-week safety evaluation period at the conclusion of MRS-TU-2019EXT treatment.

Primary Endpoint

- Change from baseline in 24-hour average ambulatory systolic blood pressure after approximately 120 days (±3) of treatment.

- To determine the response to a lower starting dose of oral SOV2012-F1 with up and down titration as appropriate, as measured by:

    - Percentage of SOV2012-F1–treated subjects with a plasma T C_{avg} within the normal range after 90 days of treatment.

Secondary Endpoints

- Change from baseline in 24-hour average ambulatory systolic blood pressure after approximately 180 days (±3) of treatment.

- Change from baseline in 7 AM to 10:30 PM -hour average ambulatory systolic blood pressure (daytime) after approximately 120 days (±3) and 180 days (±3) of treatment.
- Change from baseline in 11 PM to 6:30 AM -hour average ambulatory systolic blood pressure (nighttime) after approximately 120 days (±3) and 180 days (±3) of treatment.
- Maximum 24-hour systolic blood pressure after approximately 120 days (±3) and 180 days (±3) of treatment.
- Change from baseline in 7 AM to 10:30 PM -hour average ambulatory diastolic blood pressure (daytime) after approximately 120 days (±3) and 180 days (±3) of treatment.
- Change from baseline in 11 PM to 6:30 AM -hour average ambulatory diastolic blood pressure (nighttime) after approximately 120 days (±3) and 180 days (±3) of treatment.
- Change from baseline in 24-hour mean diastolic blood pressure (dBP) measured by ABPM
  after 120 (±3) days and 180 (±3) days of treatment, in SOV2012-F1–treated subjects.
- Maximum 24-hour diastolic blood pressure after approximately 120 days (±3) and 180 days (±3) of treatment.
- Change from baseline in 24-hour average ambulatory heartrate after approximately 120 days (±3) and 180 days (±3) of treatment.
- Change from baseline in 7 AM to 10:30 PM -hour average ambulatory heartrate (daytime) after approximately 120 days (±3) and 180 days (±3) of treatment.
- Change from baseline in 11 PM to 6:30 AM -hour average ambulatory heartrate (nighttime) after approximately 120 days (±3) and 180 days (±3) of treatment.
- Observed and change from baseline in half hourly systolic blood pressure, diastolic blood pressure, and heartrate after approximately 120 days (±3) and 180 days (±3) of treatment.
- The percentage of SOV2012-F1–treated subjects with maximum plasma testosterone concentration (T C_{max}) values after 90 days of treatment:
  - < 1500 ng/dL;
  - > 1800 to ≤ 2500 ng/dL;

- > 2500 ng/dL.

Safety Endpoints

- To determine the incidence of AEs, SAEs, and AEs leading to MRS-TU-2019EXT study withdrawal in SOV2012-F1-treated subjects.
- Observed and change from baseline in BP and HR obtained in-clinic during the treatment period.
- Observed and change from baseline in the following laboratory parameters in SOV2012-F1–treated subjects during the treatment period:
  - Liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, alkaline phosphatase)
  - Hematology parameters (hemoglobin)
  - Hormone levels (luteinizing hormone [LH], follicle-stimulating hormone [FSH], DHT, sex hormone–binding globulin [SHBG], and thyroid- stimulating hormone [TSH])
  - Lipid profiles (high-density lipoproteins, low-density lipoproteins, total cholesterol, and triglycerides)
  - Serum PSA

SOV2012-F1 Dose

Titration

The dose of study drug will be titrated during the efficacy period using an algorithm that was developed using 90-day 24-hr PK data obtained from 133 ongoing MRS-TU-2019 subjects in the SOV2012-F1 treatment group. Dose titration for each subject will be based
on the plasma T measured between 3 to 5 hours (±10min) after the morning dose at Visit 8E (Day 14E) and Visit 10E (Day 42E). Dose titrations will occur at Visit 9E (Day 28E) and Visit 11E (Day 56E) if needed, based on the following algorithm:

- For subjects who may need dose titration at Visit 9E (Day 28E) based on the plasma T level obtained between 3 to 5 hours on Visit 8E (Day 14E):
  - $T_{3\text{-}5} < 400$ ng/dL: dose increased to 600 mg (300 mg AM, 300 mg PM)
  - $T_{3\text{-}5} \geq 400$ to ≤ 900 ng/dL: no dose change
  - $T_{3\text{-}5} > 900$ ng/dL: dose decreased to 200 mg (100 mg AM, 100 mg PM)
- For subjects who may need dose titration at Visit 11E (Day 56E), based on the plasma T level obtained between 3 to 5 hours on Visit 10E (Day 42E):

- For subjects whose dose was not titrated previously (i.e., remained at 200 mg AM, 200 mg PM) and the resulting plasma $T_{3\text{-}5}$ at Visit 10E (Day 42E) are:
  - $T_{3\text{-}5} < 400$ ng/dL: dose increased to 600 mg (300 mg AM, 300 mg PM)
  - $T_{3\text{-}5} \geq 400$ to ≤ 900 ng/dL: no dose change
  - $T_{3\text{-}5} > 900$ ng/dL: dose decreased to 200 mg (100 mg AM, 100 mg PM)
- For subjects whose dose was previously decreased to 200 mg (100 mg AM, 100 mg p.m.), and the resulting plasma $T_{3\text{-}5}$ at Visit 10E (Day 42E) are:
  - $T_{3\text{-}5} < 400$ ng/dL: dose increased to 400 mg (200 mg AM, 200 mg PM)
  - $T_{3\text{-}5} \geq 400$ to ≤ 900 ng/dL: no dose change
  - $T_{3\text{-}5} > 900$ ng/dL: dose decreased to 100mg AM only.
- For subjects whose dose was previously increased to 600 mg (300 mg AM, 300 mg PM), and the resulting plasma $T_{3\text{-}5}$ at Visit 10E (Day 42E) are:
  - $T_{3\text{-}5} < 400$ ng/dL: dose increased to 800 mg (400 mg AM, 400 mg PM)
  - $T_{3\text{-}5} \geq 400$ to ≤ 900 ng/dL: no dose change
  - $T_{3\text{-}5} > 900$ ng/dL: dose decreased to 400 mg (200 mg AM, 200 mg PM)

Efficacy, Pharmacokinetics, Safety

Please refer to MRS-TU-2019 main study protocol, Section 9 for information regarding these sections.

H. STATISTICAL ANALYSIS

Sample Size and Power

Blood pressure:

The estimated standard deviation of the differences in the 24-hour mean systolic BP obtained at 90 days post-treatment and after 8 weeks of drug washout is 10mm Hg (standard deviation estimate obtained from Clarus Briefing Document, p. 62, January 9th, 2018 Meeting of the Bone, Reproductive, and Urinary Drugs Advisory Committee).

Assuming that we will have approximately135 evaluable subjects, this sample size of 135 can produce a two-sided 90% CI with a distance from the difference in means to the limits that is equal to 1.4 mm Hg when the estimated standard deviation is 10 mm Hg.

Efficacy:

With respect to sample size justification of Cavg, please refer to Section 10.2 Since the intended number of evaluable subjects for the extension study is greater than 125 targeted in the MRS-Tu-2019 study, the extension study should have adequate number of subjects to achieve the objectives regarding the endpoints of Cavg and Cmax.

Serum T/DHT Substudy

Serum samples will be collected from approximately 100 subjects with respect to Day 90E within the extension phase. This will be done using all consenting subjects within a subset of sites (sites to be chosen by the sponsor).

Analysis Populations

Statistical analyses will be performed on the following populations:

- Safety Population as defined previously in section 10.2. Note that safety analyses will be over both study phases and broken out by the extension phase and also separately for the washout and the treated periods within the extension phase.
- Extension Treated Set (EXTS): This consists of anyone that took at least 1 dose of SOV2012-F1 within the extension phase. This will be used for all analyses related to the ambulatory blood pressure and heartrate. This will also be used for the primary analysis of C_{avg}.
- Extension Efficacy Completers Set (EXCS): This population consists of all subjects who have evaluable C_{avg} and C_{max} from the 24-hour PK assessment obtained at Visit 12E, Day 90E, and no significant protocol deviations.
- Extension PK Set (EXPK): The EXPK population consists of all subjects in the study who have at least 1 evaluable 24-hr PK profile within the extension phase (calculable C_{max} or C_{avg}) and no significant protocol deviations.

- Extension Serum Set (EXSE): The EXSE population consists of all subjects in the study who have at least 1 evaluable PK profile within the extension phase (calculable C_{max} or C_{avg}), no significant protocol deviations, and samples collected for serum T/DHT quantification.

General Statistical Considerations

In general, continuous variables will be presented using descriptive statistics (number of observations [n], mean, standard deviation, standard error of mean, median, and minimum and maximum values) and categorical values will be summarized with counts and percentages.

All collected data will be presented in listings.

Baseline for the extension phase are the assessments taken just prior to dosing at Visit 7E (Day 1E) unless otherwise specified. Baseline for 24 averages will also be the 24-hour average. Baseline for hourly or half-hourly assessments will be time matched.

Primary Analyses

Efficacy (C_{avg})

The primary efficacy endpoint is the percentage of SOV2012-F1–treated subjects with a 24- hour total T C_{avg} within the normal range after 90 days of treatment within the extension. The EXTS will be the primary analysis population for efficacy.

The C_{avg} will be calculated as area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) divided by the actual number of hours between dosing and the 24-hour sample collection time. AUC_{0-24}, AUC_{0-12} and AUC_{12-24} will be calculated using noncompartmental methods. The percentage of subjects randomized to SOV2012-F1 whose 24-hour C_{avg} is within the normal range for total T will be calculated. Missing C_{avg} values will be imputed using multiple imputation procedures. The SAP will describe the methodology for multiple imputation in detail.

A 95%, 2-sided, binomial CI surrounding the point estimate will be calculated. The study will have shown effectiveness of SOV2012-F1 if at least 75% of the EXTS population has total T in the normal range and if the lower bound of the 2-sided 95% CI for that proportion is $\geq 65\%$.

A sensitivity analysis will be performed using the EXCS. In addition, using the EXTS worst-case scenario analysis will be provided.

Safety

Ambulatory Systolic Blood Pressure (sBP)

The change from baseline in the 24-hour average sBP will be analyzed as the primary blood pressure endpoint. Key secondary analyses will be derived from the changes from baseline in the daytime and night time sBP. Using the EXTS, only subjects with both a baseline (Visit 6E /Visit 7E) and the four month post baseline assessment (Visit 13E /Visit 14E) will be evaluated. No imputation methods will be employed.

The average values will be summarized by visit using summary statistics for continuous variables. Changes from baseline will also be summarized in the same way, including 90% CIs for the mean change from baseline.

The effect on sBP will be descriptively and visually evaluated using boxplots, cumulative distribution curves of 24-hour averages and forest plots of daytime average, nighttime average, and 24-hour average change from baseline with 95% confidence intervals.

Maximum sBP and time matched changes will be summarized for baseline and each visit.

Shift tables using pre-defined ranges will be used in evaluating the maximum sBP within a 24-hour period, and also daytime and nighttime separately. Maximum time matched changes will be evaluated in a similar fashion.

In addition, a mixed model analysis with subject as a random effect and visit (EXTS baseline as reference, and the four month post baseline as test), prior randomized treatment in MRS- TU-2019, and history of hypertension (and whether treated or not treated) as fixed effects.

Additional effects such as the presence of diabetes mellitus will be considered for inclusion.

A six month (Visit 15E/Visit 16E) evaluation of ambulatory blood pressure will also be performed. Further details will be provided in the SAP.

The difference in least squares means and associated 90% CI will be provided. Goodness of fit will be evaluated.

Secondary Analyses

Ambulatory Diastolic blood pressure (dBP) and Ambulatory heartrate (HR)

These will be evaluated in a similar fashion to the sBP except for the maximum heartrate.

Hourly and half hourly observed and time matched change from baseline will be descriptively summarized.

Graphical display overlays of half hour and hourly ABPM averages that include standard deviation bars for sBP, dBP and heartrate will be generated.

C_{max}

T C_{max} after 90 days of treatment within the extension phase will be evaluated. EXTS will be the primary analysis population.

The secondary endpoint will be evaluated by estimating the proportion of SOV2012-F1 treated subjects at Visit 12E, Day 90E with:

a) T $C_{max} \leq 1500$ ng/dL
b) T $C_{max} > 1800$ and ≤ 2500 ng/dL
c) T $C_{max} > 2500$ ng/dL

Subgroup Analysis

As data permits, subgroup analyses of sBP and dBP will be performed focusing on hypertension treated, with hypertension untreated, without hypertension, and with and without diabetes mellitus.

Pharmacokinetic Analysis

Using the EXPK the following evaluations will be performed:

- The percentage of male hypogonadal subjects with T C_{avg} within the normal range after 90 days of treatment.
- The percentage of SOV2012-F1–treated subjects with maximum plasma testosterone concentration (T C_{max}) values:
  - < 1500 ng/dL;
  - > 1800 to ≤ 2500 ng/dL;
  - > 2500 ng/dL.

Bioanalytical Analysis

Using the EXPK, the T and DHT values obtained from plasma NaF/EDTA tube samples will be evaluated using regression analysis to determine the relationship between T and DHT values.

Safety Analysis

Using the Safety Population, treatment emergent adverse events (TEAEs) will be summarized for the entire study combined, and also for the extension only by period (washout and treatment) and tabulated by system organ class (SOC) and preferred term.

Observed values collected in clinic vital sign measurements, including sBP, dBP, HR, and body weight, and changes from extension baseline in sBP, dBP, HR, and body weight will be summarized by extension phase visit and treatment.

Observed values and changes from extension baseline in laboratory test results will be summarized by extension visit. Shift tables will be used to evaluate changes in laboratory test values with respect to normal reference range.

Serum T/DHT

Using the EXSE, exploratory analyses may be performed that would evaluate further the relationship of the assay methods in terms of titration concordance and primary and secondary endpoints.

Titration Decisions

Using the T concentrations obtained at the titration timepoints with EDTA and serum tubes, exploratory analysis may be performed to compare the predicted titration decisions with those which were made using NaF-EDTA samples.