Statistical Analysis Plan

Sponsor Name:	**Marius Pharmaceuticals**
Protocol Number and Title:	**MRS-TU-2019: A 12-Month, Randomized, Active-controlled, Open-label Study of the Efficacy and Safety of Oral Testosterone Undecanoate in Hypogonadal Men** **and** **MRS-TU-2019EXT: Ambulatory Blood Pressure Monitoring (ABPM) Extension Study**
Protocol Versions and Dates:	**Version 1.0 01MAR2017** **Version 2.0 10MAY2017** **Version 3.0 15JUN2017** **Version 4.0 08AUG2017** **Version 5.0 18AUG2017** **Version 6.0 19JAN2018** **Version 7.0 27JUN2018** **Version 8.0 09OCT2018** **Version 9.0 18FEB2019**
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I confirm that I have reviewed this document and agree with the content.

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AAS	ACTH Analysis Set
ABPM	Ambulatory Blood Pressure Monitoring
ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ASA24	Automated Self-Administered 24-Hour Recall
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Concentration vs. Time Curve
BLQ	Below the Limit of Quantification
BMI	Body Mass index
BP	Blood Pressure
BSSS	Bioanalytical Sample Stability Sub-Study
bpm	Beats per Minute
C_{avg}	Average Concentration
CI	Confidence Interval
C_{max}	Maximum Concentration
CSR	Clinical Study Report
CV	Coefficient of Variation
C_x	Concentration at x hours after morning dose
dBP	Diastolic Blood Pressure
DRM	Data Review Meeting
DHT	Dihydrotestosterone
DHTU	Dihydrotestosterone Undecanoate
E2	Estradiol
ECG	Electrocardiogram

Abbreviation	Description
eCRF	Electronic Case Report Form
ECS	Efficacy Completers Set
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
EOT	End of Treatment
EXPK	Extension Pharmacokinetic Set
EXSE	Extension Serum Set
EXTS	Extension Treated Set
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GI	Gastrointestinal
HGB	Hemoglobin
HR	Heart Rate
ICH	International Conference on Harmonization
IIEF	International Index of Erectile Function Questionnaire
I-PSS	International Prostate Symptom Score
LC-MS	Liquid Chromatography-Mass Spectrometry
LH	Luteinizing Hormone
LLN	Lower Limit of Normal
MACE	Major Adverse Cardiac Events
MAP	Mean Arterial Pressure
MAR	Missing at Random
Max	Maximum
MCS	Mental Component Summary Score
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MS	Mass Spectrometry
n	Number of Non-Missing Observations

Abbreviation	Description
N/A	Not Applicable
nBLQ	Number of Values Below BLQ
OSS	Overall Safety Set
PCS	Physical Component Summary Score
PD	Protocol Deviation
PDQ	Psychosexual Daily Questionnaire
PK	Pharmacokinetic(s)
PKS	PK Set
PP	Pulse Pressure
PSA	Prostate-Specific Antigen
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sBP	Systolic Blood Pressure
SD	Standard Deviation
SF-36	Short Form Survey
SHBG	Sex Hormone–binding Globulin
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
T	Testosterone
TB	Total Bilirubin
T C_{avg}	Average Total Testosterone
T C_{max}	Maximum Total Testosterone
T $C_{predose}$	T Predose Concentration
TEAE	Treatment-Emergent Adverse Event

Abbreviation	Description
T_{max}	Time to C_{max}
T_{last}	Last Timepoint
TLF	Table, Listing and Figure
TRT	Testosterone Replacement Therapy
TSH	Thyroid-Stimulating Hormone
TU	Testosterone Undecanoate
ULN	Upper Limit of Normal
WCS	Worst-Case Scenario
WHO	World Health Organization

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. RESPONSIBILITIES

Pharstat Inc. will perform the final statistical analyses and are responsible for the production and quality control of all tables, figures and listings as outlined within this SAP. Final pharmacokinetic (PK) analysis will be carried out by Pharstat Inc. as outlined within this SAP.

2.2. TIMINGS OF ANALYSES

An informal interim analysis of the primary and secondary efficacy data, PK, and safety was conducted after all subjects had completed the 90-day visit in MRS-TU-2019 or had terminated early from the efficacy period of the MRS-TU-2019 study. The final analysis of all study data will be conducted when all subjects complete their final post-treatment follow-up visit. In addition, Study MRS-TNR2019 (for normal range assessment) will have completed with topline results prior to any analyses under MRS-TU-2019EXT.

3. STUDY OBJECTIVES

3.1. MRS-TU-2019 OBJECTIVES

3.1.1. Primary Objective

The primary objective of the MRS-TU-2019 study is to determine the efficacy of oral SOV2012-F1 as measured by the percentage of male hypogonadal subjects with T C_{avg} within the normal range after 90 days of treatment.

3.1.2. Secondary Objective

This secondary objective has been updated to reflect FDA feedback:

The secondary objective of the MRS-TU-2019 study is to determine the percentage of SOV2012-F1–treated subjects with T Cmax values (a) ≤1.5 x ULN; (b) 1.800 x ULN to 2.5 x ULN ; and (c) >2.5 x ULN after 90 days of treatment, where the ULN is defined using the NaF/EDTA plasma and serum endogenous testosterone from study MRS-TNR2019.

3.1.3. Exploratory Objectives

The exploratory objectives of the MRS-TU-2019 study are:

- To determine the change from baseline in the following subject-reported outcomes by SOV2012-F1–treated and AndroGel-treated subjects in International Prostate Symptom Score (I-PSS), Psychosexual Daily Questionnaire (PDQ), Short Form Survey (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 testosterone undecanoate (TU) orally, including three types of plasma tubes (EDTA, NaF/EDTA, and lithium heparin).

3.1.4. Safety Objectives

The safety objectives of the MRS-TU-2019 study are:

- To determine the incidence of adverse events (AEs), serious 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 blood pressure (BP), liver function tests, hematology parameters, hormone levels, lipid profiles, and serum 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 adrenocorticotropic hormone (ACTH) at baseline and after 52 weeks of treatment in a subset of 30 SOV2012-F1 subjects and 15 AndroGel subjects.

3.2. MRS-TU-2019EXT OBJECTIVES

3.2.1. Primary Objectives

- To assess change from baseline in 24-hour mean sBP measured by ambulatory BP monitoring (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 T C_{avg} within the normal range after 90 days of treatment.

3.2.2. Secondary Objectives

To determine the response to a lower starting dose (and revised titration thresholds) of oral SOV2012-F1 with up and down titration as appropriate, as measured by:

- *This secondary objective has been updated to reflect FDA feedback:* To determine the percentage of SOV2012-F1–treated subjects with T Cmax values (a) ≤1.5 x ULN; (b) 1.800 x ULN to 2.5 x ULN; and (c) >2.5 x ULN after 90 days of treatment, where the ULN is defined using the NaF/EDTA plasma and serum endogenous testosterone from study MRS-TNR2019.

- To assess change from baseline in 24-hour mean 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 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 (NaF/EDTA).

3.2.3. Safety Objectives

- To assess hematology parameters, hormone levels, lipid profiles, and serum PSA in SOV2012-F1–treated subjects after 180 days of treatment.
- To determine the incidence of AEs, SAEs, and AEs leading to study withdrawal in SOV2012-F1-treated subjects after 180 days of treatment.

3.3. BRIEF DESCRIPTION

3.3.1. MRS-TU-2019

This study is a Phase 3, randomized, multicenter, open-label, active-controlled, efficacy 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.

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.

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 after the morning dose at Visit 4, Day 14 and Visit 6, Day 42 will determine the need, if any, to titrate 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 (Section 16.4 of study protocol) 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 on Day 166 and Day 256, respectively. 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.

To determine any effect of the phytosterols in SOV2012-F1 on adrenal cortical function, ACTH stimulation testing will be performed and the serum cortisol response to synthetic ACTH will be measured at baseline (Visit 3) and the End-of-Treatment visit in a subset of subjects. At randomization, 45 subjects (2:1 ratio of SOV2012-F1 to AndroGel subjects) will be enrolled to the ACTH sub-study to ensure 30 subjects are available for assessment at the End of Treatment (EOT) visit (Day 365). Synthetic ACTH1-24 (cosyntropin)

will be administered to these subjects intravenously at Time 0 and blood for serum cortisol will be obtained before and 30 and 60 minutes after cosyntropin administration.

The schema in **Figure 1** and **Figure 2** depict the plan described in the protocol for the SOV2012-F1 and the AndroGel groups, respectively.

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

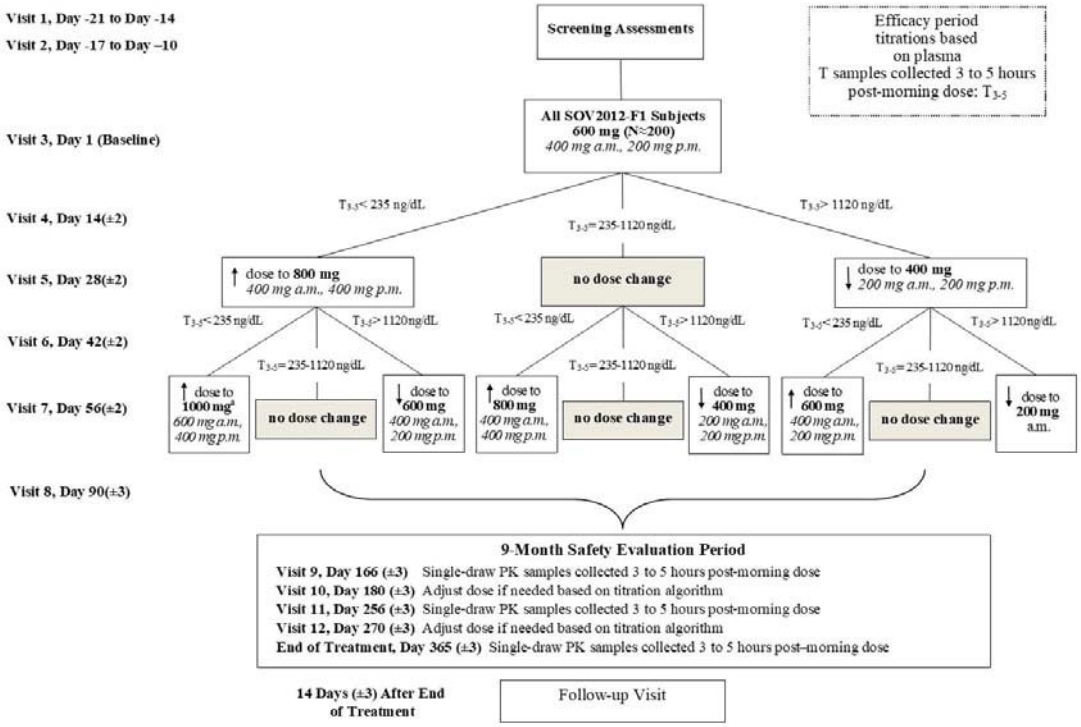
- A SOV2012-F1–treated subject has been previously down-titrated to 200 mg in the morning only, and T C_{max} is >2500 ng/dL on Day 90: the subject will be withdrawn, as continuation in the study will expose the subject to repeated T C_{max} values >2500 ng/dL.

- 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 withdrawn 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.

Subjects who discontinue study drug will be asked to complete the procedures of an EOT visit.

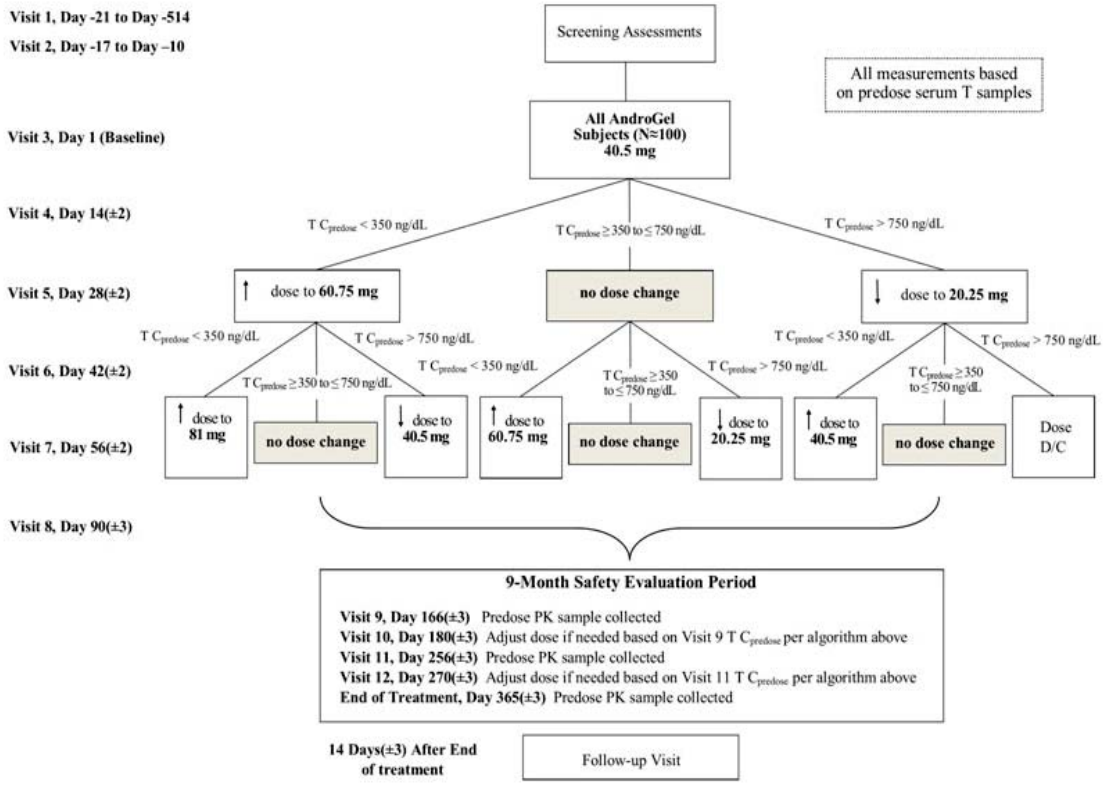
Figure 1: Overall Study Design, SOV2012-F1 Group



Abbreviations: a m. = morning; N = number of subjects; p.m. = evening; T_{3-5} = plasma T concentration measured between 3 and 5 hours 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 (CSR).

Figure 2: Overall Study Design, AndroGel Group



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

3.3.2. MRS-TU-2019EXT

Study MRS-TU-2019EXT is a second study following MRS-TU-2019. One purpose is to further examine the BP effects of Marius's oral TU formulation, SOV2012-F1, using 24-hour 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]), revised titration thresholds and using strengths of 100, 150 and 200 mg TU to further enhance drug administration. To distinguish the two studies, study days and visits in MRS-TU-2019EXT are designated with 'E', e.g. Day 120E or Visit14E or V14E.

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 MRS-TU-2019EXT study. Eligible men who have

consented to this MRS-TU-2019EXT study will be withdrawn from TRT for a minimum of 8 weeks following their conclusion of MRS-TU-2019.

Continuing Subjects: Subjects completing the MRS-TU-2019 study and going directly into MRS-TU-2019EXT complete the MRS-TU-2019EXT study defined 8-week washout and begin a total of 180 days of treatment on SOV2012-F1. These subjects have an initial ABPM assessment on Day 364/365 of MRS-TU-2019.

Late Entry Subjects: 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 assessment. These late entry subjects will still be required to have an 8-week washout period, beginning at time of consent. Any interim TRT between time of completion of MRS-TU-2019 and consent for MRS-TU-2019EXT, must be recorded in the electronic case report form (eCRF). These subjects must pass the ABPM evaluation at V7E/ Day 1E to continue in the ABPM MRS-TU-2019EXT study.

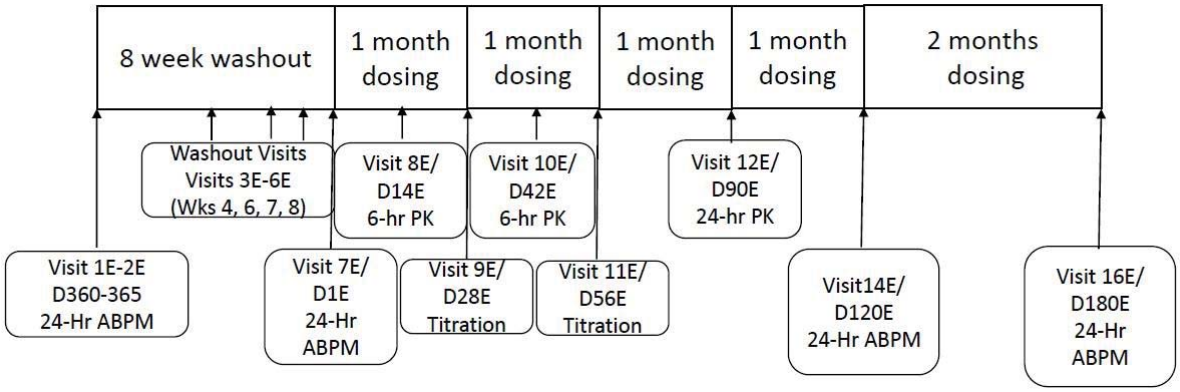
Newly Enrolling Subjects: Enrollment of subjects naïve to MRS-TU-2019 or subjects who completed the MRS-TU-2019 study more than 8 weeks prior to the start of MRS-TU-2019EXT will be permitted at a few sites in order to maximize enrollment for MRS-TU-2019EXT, provided those subjects meet both the MRS-TU-2019 and MRS-TU-2019EXT 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 MRS-TU-2019 protocol, prior to being enrolled into MRS-TU-2019EXT. See Table 4: Schedule of Assessments for ABPM MRS-TU-2019EXT Study Pre-treatment Period for Newly Enrolled Subjects (MRS-TU-2019 Naïve or Late Entry Subjects who Qualify for New Enrollment). These subjects must pass the ABPM evaluation at V7E/ Day 1E to continue in the ABPM MRS-TU-2019EXT study.

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 the treatment period using a refined dose-titration algorithm (Appendix 16.2). 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 is a Continuing Subject, or is a Late Entry Subject, or a Newly Enrolled Subject. Continuing Subjects will have an ABPM at Day 364/365 (EOT) of MRS-TU-2019 study; all MRS-TU-2019EXT subjects will have ABPM assessments at Day 1E (prior to treatment), at Day 120E and at Day 180E of treatment. The Day 180E (6-month) visit will provide data on stabilization of ambulatory BP, following the Day 120E (4-month) data for ambulatory BP primary endpoint. Note that in this SAP, ambulatory refers to ABPM.

24-hr Serum T and DHT Sub-study:

At select centers, approximately 100 subjects will participate in a 24-hr serum T sample collection sub-study conducted at Visit 12E. Subjects enrolled in the serum T sub-study 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 a.m. dose.

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 (Table 3 to Table 5).

3.4. SUBJECT SELECTION

3.4.1. Inclusion Criteria

See Protocol Section 7.3.2 for MRS-TU-2019 and Protocol Appendix 16.12 Section G for MRS-TU-2019EXT.

3.4.2. Exclusion Criteria

See Protocol Section 7.3.3 for MRS-TU-2019 and Protocol Appendix 16.12 Section G for MRS-TU-2019EXT.

3.5. DETERMINATION OF SAMPLE SIZE

3.5.1. MRS-TU-2019

To meet the criterion of the primary endpoint, the percentage 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 clinical study, Study SOV-TU-PK2013[1], 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 1 below. To yield a conservative estimate of the required sample size, the true percentage of subjects with average concentration (C_{avg}) within the normal range is estimated at 75%.

Table 1: Sample Size Estimates

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

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 subjects would have to be randomized into the SOV2012-F1 group.

Additional Food and Drug Administration (FDA) guidance requires that at least 100 subjects in the oral TU treatment arm reach 12 months of study drug exposure[2]. 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 to 2500 mg/dL is >5%. That is, with a probability of 98.5%, the percentage of subjects with maximum concentration (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[3] an estimate of intra-subject variability of the data was determined to be approximately 93 nmol/L. As such, for a two-sided 90% CI for a two-sample normal mean difference for a mixed model analysis with subject as a random effect, assuming a common SD 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 mean 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.

3.5.2. MRS-TU-2019EXT

The estimated SD of the differences in the 24-hour mean sBP obtained at 90 days post-treatment and after 8 weeks of drug washout is 10 mmHg (SD estimate obtained from Clarus Briefing Document[4], p. 62). Assuming that we will have approximately 135 evaluable subjects, this sample size of 135 subjects can produce a two-sided 90% CI with a distance from the difference in means to the limits that is equal to 1.4 mmHg when the estimated SD is 10 mmHg.

Furthermore, a sample size of 119 evaluable subjects achieves 90% power to detect non-inferiority using a one-sided one-sample t-test when the non-inferiority margin is 3.0 mmHg, the actual mean is 0, and the significance level (alpha) of the test is 0.025. Assuming a 10% unevaluable rate, 133 subjects would need to be enrolled to achieve 119 evaluable.

With respect to sample size justification of C_{avg}, please refer to Section 3.5.1. Since the intended number of evaluable subjects for the MRS-TU-2019EXT study is greater than the 125 targeted in the MRS-TU-2019 study, the MRS-TU-2019EXT study should have adequate number of subjects to achieve the objectives regarding the endpoints of C_{avg} and C_{max}.

For the serum T and DHT sub-study, serum samples will be collected from approximately 100 subjects with respect to Day 90E within the MRS-TU-2019EXT study. This will be done using all consenting subjects within a subset of sites (sites to be chosen by the sponsor).

3.6. TREATMENT ASSIGNMENT & BLINDING

Subjects eligible for MRS-TU-2019 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. At randomization, 45 subjects (2:1 ratio of SOV2012-F1 to AndroGel subjects) will be enrolled into the ACTH sub-study. At Screening Visit 1, subjects will be offered the opportunity to participate in the ACTH stimulation sub-study. The informed consent form addendum for the ACTH sub-study will be signed by Visit 2.

In MRS-TU-2019EXT, 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 study protocol (Appendix 16.2).

Blinding is not applicable (N/A); these are open-label studies.

3.7. ADMINISTRATION OF STUDY DRUG

MRS-TU-2019 uses only SOV2012-F1 200 mg TU capsules, with a starting total daily dose 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 minutes after the start of their meal.

MRS-TU-2019EXT uses three capsule strengths (100, 150 and 200 mg TU per capsule), with a starting total daily dose of 400 mg (200 mg with the breakfast meal and 200 mg with dinner meal). Subjects will be instructed to take the SOV2012-F1 capsules with water 30 minutes after the start of their meal.

In Study MRS-TU-2019, 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).

3.8. STUDY PROCEDURES AND FLOWCHART

3.8.1. MRS-TU-2019

The study consists of 2 screening visits, with screening lasting up to 21 days, 11 treatment visits, starting with Visit 3 (Day 1) and ending with the EOT visit (Day 365 or early withdrawal) and a follow-up visit (14 days after EOT).

The schedule of assessments is shown in Table 2 below.

Table 2: MRS-TU-2019 Schedule of Assessments

Assessment	Pre-		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)[a,]	End of Treatment Day 365 (+/-3)[a,*] Or 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 T, 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 [illegible][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)[a,*] 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			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 Subject Food Diary	X													

Table continues on next page.

Collect Food Diary and enter into ASA24		X												
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 BP; 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 BP; 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 laboratory 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 EOT (Day 365). At all other visits, subjects should undergo a symptom-directed physical examination.

d Vital signs include BP, HR, temperature, and weight. 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 at least 5 minutes. On all study visit days where BP is measured only once (V2) or predose (V3, V5, V7, V9-V12, EOT 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 mmHg and > 5 mmHg, 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 (TB), 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 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 T is collected. At Visit 2, the biochemistry sampling includes sample for T.

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 postdose for AndroGel-treated subjects.
o On visit days after Day 90, blood samples for AndroGel-treated subjects will be collected predose 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, (predose and 2, 4, 8, 12, 16, 20, and 24 hours postdose).
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 laboratory 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 sub-study (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 Protocol Section 8.1.2 for further details.
Bioanalytical Sample Stability Sub-study (BSSS): 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 laboratory 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-2019EXT ABPM Sub-study: Please refer to Appendix 16.12 for Schedule of Assessments for subjects participating in the MRS-TU-2019EXT study.

3.8.2. MRS-TU-2019EXT

Table 3: Schedule of Assessments for EOT MRS-TU-2019 and ABPM 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 and MRS-TU-2019EXT			MRS-TU-2019EXT ABPM Study PRE-TREATMENT WASHOUT PERIOD				
	Visit 1E[a] MRS-TU-2019EXT Day 364 (±3d); within1day prior to	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	**Visit 4E** 42 days/ 6 weeks (+3d) After Last dose MRS-TU-2019 **Or** EXT	**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
FASTING VISIT	X	X			X	X	X	X
Informed consent -E	X[s]			X[s]				
Inclusion/exclusion criteria	X			X[s]				
Concomitant	X	X	X	X	X	X	X	X
Physical examination[c]		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								
Perform accountability		X						

Table continues on next page.

	MRS-TU-2019 EOT and MRS-TU-2019EXT Study Start			MRS-TU-2019EXT ABPM Study PRE-TREATMENT WASHOUT 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 4: Schedule of Assessments for ABPM MRS-TU-2019EXT 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 Study PRE-TREATMENT Period
	NEW Subject Screening Visit 1(EXT)[t]	NEW Subject Screening Visit 2(EXT)[t]	Visit 6E (Within 10days of Visit 2(EXT) (and 1d prior to Visit
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[c]		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 T, 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			X
Distribute ABPM Unit for MRS-TU-2019EXT			X

Table 5: Schedule of Assessments for ABPM MRS-TU-2019EXT Study Treatment Period for All Subjects

	MRS-TU-2019EXT ABPM 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[c]	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 (predose)											
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						

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	MRS-TU-2019EXT ABPM 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 Sub-study Subjects[u]						X[u]						
E2 (Single or 24-hour PK), SOV2012-F1[k]	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 postdose)		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 BP 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 = T undecanoate; WBC = white blood cells; WD = withdrawal

a. Visit applies to the MRS-TU-2019EXT ABPM 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 laboratory results should be available.
c. Full physical examination must include assessment for the presence of gynecomastia, and digital rectal examination at EOT in MRS-TU-2019 (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, HR, temperature, and weight. 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 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 (+5 min) apart in the sitting position with the arm supported at the heart level (mid-chest height). 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, TB, creatinine, BUN, eGFR, LDH, glucose, total protein, albumin, sodium, potassium, calcium, and phosphorus. At Visit 7/Day 1E the laboratory samples will be obtained predose 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 sub-study in MRS-TU-2019 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 MRS-TU-2019EXT: PK samples are collected pre-morning dose and 1.5, 3, 4, 5, and 6 hours, after a m. 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 a m. 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 3-5 hours (+10min) post-morning dose**. 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 laboratory samples at EOT / Day 365 / Visit 2E, and on Visit 7E / Day 1E. Breakfast (MRS-TU-2019 ASA-assigned meal type) is required on Visits 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%, or 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-2019EXT subjects who do not qualify for new enrollment:** Subjects who already completed D365 of the MRS-TU-2019 study 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 28 days (4 weeks) 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-24-hr 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 MRS-TU-2019, and completed MRS-TU-2019 >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 sub-study subjects** should have serum T drawn at all 24-hr 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 a.m. dose.

4. ENDPOINTS

4.1. MRS-TU-2019 ENDPOINTS

4.1.1. Primary Endpoint

The primary endpoint of the MRS-TU-2019 study is the percentage of SOV2012-F1–treated subjects with a 24-hour T C_{avg} within the normal range after 90 days of treatment.

Serum T C_{avg} values for those subjects randomly assigned to receive AndroGel will be summarized only.

4.1.2. Secondary Endpoints

Other endpoints of the MRS-TU-2019 study are the percentage of SOV2012-F1-treated subjects at Day 90 (Visit 8) with plasma T C_{max} values that are:

- *≤1.5 x ULN;*
- *1.8 x ULN to 2.5 x ULN; and*
- *>2.5 x ULN where the ULN is defined using the NaF/EDTA plasma and serum endogenous testosterone from study MRS-TNR-2019.*

Serum T C_{max} values for those subjects randomly assigned to receive AndroGel will be summarized using the following ranges (ng/dL):

- *≤1500;*
- *1800 to 2500; and*
- *>2500.*

These endpoints will be reported as safety endpoints.

4.1.3. Exploratory Endpoints

The exploratory efficacy endpoints of the MRS-TU-2019 study are:

- Change from baseline in the following subject-reported outcomes by SOV2012-F1-treated and AndroGel-treated subjects, after 52 weeks of treatment:

- I-PSS;
- PDQ;
- SF-36;
- IIEF.

- Change from baseline in fasting serum 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.

4.1.4. Safety Endpoints

The safety endpoints for the MRS-TU-2019 study include the following:

- Incidence of AEs, SAEs, drug-related AEs and AEs leading to study withdrawal in SOV2012-F1–treated subjects compared with AndroGel-treated subjects after 52 weeks of treatment.

- Observed and change from baseline in sBP and dBP and HR.

- Safety biochemistry and hematology laboratory evaluations including but not limited to the following:

  - Liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin (TB), alkaline phosphatase [ALP]).

  - 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.

- Serum cortisol response to intravenous administration of synthetic ACTH.

4.2. MRS-TU-2019EXT ENDPOINTS

4.2.1. Primary Endpoints

The primary ABPM endpoint is the change from baseline in 24-hour average ambulatory sBP after approximately 120 (±3) days of treatment.

The primary efficacy endpoint, to determine the response to a lower starting dose of oral SOV2012-F1 with up and down titration as appropriate, is the percentage of SOV2012-F1-treated subjects with a plasma T C_{avg} within the normal range after 90 days of treatment.

4.2.2. Secondary Endpoints

Other endpoints are:

- Percentage of subjects with T C_{max} values after 90 days of treatment:
    - *≤1.5 x ULN;*
    - *1.8 x ULN to 2.5 x ULN; and*
    - *>2.5 x ULN* where the ULN is defined using the NaF/EDTA plasma and serum endogenous testosterone from study MRS-TNR-2019.
- Change from baseline in 24-hour average ambulatory sBP after approximately 180 (±3) days of treatment.
- Change from baseline in 7 a.m. to 10:30 p.m. -hour average ambulatory sBP (daytime) after approximately 120 (±3) days and 180 (±3) days of treatment.
- Change from baseline in 11 p.m. to 6:30 a.m. -hour average ambulatory sBP (nighttime) after approximately 120 (±3) days and 180 (±3) days of treatment.
- Change from baseline in 24-hour mean dBP measured by ABPM after 120 (±3) days and 180 (±3) days of treatment.
- Change from baseline in 7 a.m. to 10:30 p.m. -hour average ambulatory dBP (daytime) after approximately 120 (±3) days and 180 (±3) days of treatment.
- Change from baseline in 11 p.m. to 6:30 a.m. -hour average ambulatory dBP (nighttime) after approximately 120 (±3) days and 180 (±3) days of treatment.

- Change from baseline in 24-hour average ambulatory HR after approximately 120 (±3) days and 180 (±3) days of treatment.

- Change from baseline in 7 a.m. to 10:30 p.m. -hour average ambulatory HR (daytime) after approximately 120 (±3) days and 180 (±3) days of treatment.

- Change from baseline in 11 p.m. to 6:30 a.m. -hour average ambulatory HR (nighttime) after approximately 120 (±3) days and 180 (±3) days of treatment.

- Observed and change from baseline in half-hourly sBP, dBP, and HR after approximately 120 (±3) days and 180 (±3) days of treatment.

4.2.3. Safety Endpoints

- To determine the incidence of AEs, SAEs, and AEs leading to MRS-TU- 2019EXT study withdrawal.

- Observed and change from baseline in BP and HR obtained in-clinic during the treatment period.

- Observed, change from baseline, and percent change from baseline in the following laboratory parameters during the treatment period:

    - Liver function tests (ALT, AST, TB, ALP)

    - 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

4.3. PHARMACOKINETIC (PK) ENDPOINTS

PK assessments include the concentration data and calculation of PK parameters for:

- Plasma total T and DHT for SOV2012-F1 subjects measured at Days 14, 42, 90 and 90E in NaF/EDTA tubes.

- Serum total T and DHT for SOV2012-F1 subjects measured at Day 90E.

- Plasma TU, DHT undecanoate (DHTU), and E2 for SOV2012-F1 subjects measured at Day 90 and Day 90E in NaF/EDTA tubes.
- Serum total T, DHT, and plasma E2 for AndroGel subjects measured at Day 90, if applicable.

PK Parameters:

- Maximum concentration (C_{max})
- Time to maximum concentration (T_{max})
- Area under the concentration-time curve from Time 0 to 24 hours (AUC_{0-24})
- 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 24 hours (C_{avg})
- Average concentration from Time 0 to 12 hours ($C_{avg0-12}$)
- Average concentration from Time 12 to 24 hours ($C_{avg12-24}$)
- DHT/T and E2/T ratios calculated on $C_{avg,}$ AUC_{0-12}, and AUC_{12-24}
- Calculated free T concentration at MRS-TU-2019 baseline, MRS-TU-2019EXT baseline, Day 90 and Day 90E (methods in Section 9.4.1)

Additional parameters may be calculated if deemed necessary and useful for data interpretation.

5. ANALYSIS SETS

For MRS-TU-2019, the Safety Set (SS), Full Analysis Set (FAS), Pharmacokinetic Set (PKS), and Efficacy Completers Set (ECS) were defined and finalized at a data review meeting (DRM) after data cleaning was complete for the interim analysis. The ACTH Analysis Set (AAS) will be finalized at a DRM after data cleaning is complete for the final analysis.

For MRS-TU-2019EXT, the Extension Treated Set (EXTS), the Modified Extension Treated Set (mEXTS), the Extension Pharmacokinetic (EXPK) Set, the Extension Serum (EXSE) Set, and the Modified Extension Serum (mEXSE) Set will be defined and finalized at a DRM after data cleaning is complete for the final analysis.

The Overall Safety Set (OSS), which consists of subjects from both studies who took at least one dose of SOV2012-F1, will be finalized at a DRM after data cleaning is complete for the final analysis.

5.1. MRS-TU-2019 ANALYSIS SETS

5.1.1. Safety Set (SS)

The SS will include all subjects who took at least one dose of study drug (SOV2012-F1 or AndroGel) in MRS-TU-2019. Note that MRS-TU-2019 AE analyses will include the washout period before the first dose of SOV2012-F1 in MRS-TU-2019EXT for continuing subjects and late entry subjects.

5.1.2. Full Analysis Set (FAS)

The FAS will include all subjects randomized into the study who received at least one dose of correctly assigned study drug. The primary analyses for the primary and secondary MRS-TU-2019 endpoints will be performed on the FAS.

5.1.3. Pharmacokinetic Set (PKS)

The PKS will include all subjects in the study who received at least one dose of study drug and at least one evaluable PK profile within MRS-TU-2019 (calculable C_{max} and C_{avg}) and no significant protocol deviations (PDs).

5.1.4. Efficacy Completers Set (ECS)

The ECS will include all subjects in the PKS who have evaluable C_{avg} and C_{max} from the 24-hour PK assessment obtained at Visit 8, Day 90, and no significant PDs.

5.1.5. ACTH Completer Analysis Set (AAS)

The AAS will include all subjects randomized into the ACTH sub–study who received correctly assigned study drug (including synthetic ACTH1-24 [cosyntropin]) and who had serum cortisol results at Visit 3 and Day 365 (end of treatment).

5.2. MRS-TU-2019EXT ANALYSIS SETS

5.2.1. Subject Sources

Continuing

Subjects completing the MRS-TU-2019 study and going directly into MRS-TU-2019EXT, completing the MRS-TU-2019EXT study defined 8-week washout, and beginning a total of 180 days of treatment on SOV2012-F1. These subjects will have participated in a Day 364/365 (Visit 1E) ABPM assessment. These subjects must have a successful ABPM assessment at Visit 6E/7E to continue in the study.

Late Entry

Subjects having a gap between completion of MRS-TU-2019 and entry into the MRS-TU-2019EXT study who will complete 8 weeks of washout from time of consent and then begin 180 days of treatment on SOV2012-F1. These subjects completed Day 365 in MRS-TU-2019 prior to the start of MRS-TU-2019EXT thus bypassing the Day 364/365 ABPM MRS-TU-2019EXT study assessment.

New Enrollment

These are subjects naïve to MRS-TU-2019 or subjects who have completed the MRS-TU-2019 study more than 8 weeks prior to the start of MRS-TU-2019EXT. These subjects would need to complete Screening Visit 1 (EXT) and Screening Visit 2 (EXT) prior to being enrolled into MRS-TU-2019EXT.

5.2.2. Extension Treated Set (EXTS)

The EXTS will include all subjects who took at least one dose of SOV2012-F1 within MRS-TU-2019EXT. This analysis set will be used for all analyses related to the ambulatory BP, and the ambulatory HR.

Modified EXTS (mEXTS)

The modified EXTS consists of the EXTS excluding Site 104. Reasons for excluding Site 104 are documented in Appendix 16.4. This analysis set will be used for the primary analysis of C_{avg}, and the analysis of C_{max}

5.2.3. Extension Pharmacokinetic (EXPK) Set

The EXPK Set consists of all subjects in the study who received at least one dose of SOV2012-F1, have at least 1 evaluable 24-hr PK profile within MRS-TU-2019EXT (calculable Cmax or Cavg) and no significant protocol deviations. Site 104 is excluded from the EXPK Set. Reasons for excluding Site 104 are documented in Appendix 16.4.

5.2.4. Extension Serum (EXSE) Set

The EXSE population consists of all subjects in the study who consented to the serum substudy and took at least one dose of SOV2012-F1 within MRS-TU-2019EXT.

Modified EXSE (mEXSE)

The modified EXTS consists of the EXSE excluding Site 104. Reasons for excluding Site 104 are documented in Appendix 16.4.

5.3. OVERALL ANALYSIS SET

5.3.1. Overall Safety Set (OSS)

The OSS will include all subjects who took at least one dose of SOV2012-F1 in MRS-TU-2019 and/or MRS-TU-2019EXT. This analysis set will be used for pooled analysis of all subjects exposed to SOV2012-F1.

5.4. PROTOCOL DEVIATIONS (PDS)

PDs will be addressed during study monitoring on an ongoing basis. All PDs will be recorded in the clinical trial management system.

5.4.1. Data Review Meeting (DRM)

A review of all PDs from MRS-TU-2019 and MRS-TU-2019EXT will be performed on an ongoing basis to categorize each one as significant (with a potential impact on the efficacy and/or PK evaluation) or not significant and identify the subjects that should be excluded from any of the relevant analysis sets. Each PD will be assigned as significant or not significant by the Study Management Team, in cooperation with Data Management, Biostatistics, Medical Monitoring, and the Sponsor. These data will then be imported into SAS®.

All decisions made at the DRM will be documented in the DRM highlights. The final list of PDs including the decisions on analysis sets made in the meeting will be appended to the highlights. Approval of the DRM

highlights will be confirmed by the signatures of the Lead Biostatistician, the Project Leader and a Marius Pharmaceuticals representative.

5.4.2. PDs General

- A PD will be considered related to MRS-TU-2019 if it occurs at any time before Visit 1E (Day 364) for a continuing subject or if it occurs at any time before MRS-TU-2019EXT late entry consent for a late entry subject.

- A PD will be considered related to MRS-TU-2019EXT if it occurs on or after Visit 1E (Day 364) for a continuing subject or if it occurs at or after MRS-TU-2019EXT late entry consent for a late entry subject.

- Missing and partial PD start dates will be reviewed to determine if relationship to study can be assigned.

- All PDs will be listed for all subjects in the SS and EXTS, including their assignment of significant or not significant.

- Significant PDs will be summarized by deviation type, for all subjects in the OSS and for all subjects who took SOV2012-F1 in both studies.

5.4.3. Signficant Protocol Deviations: MRS-TU-2019

Examples of significant PDs leading to exclusion from the PKS and ECS are:

- Taking prohibited 5 alpha-reductase inhibitors.

- SOV2012-F1 subjects meeting Exclusion Criterion 10 (relevant gastrointestinal [GI] surgery).

- Not completing a single confinement visit.

Additional significant PDs leading to exclusion from the PKS are:

- SOV2012-F1 subjects with major PDs in dosing meal at both breakfast and dinner at all 3 confinement visits.

Additional significant PDs leading to exclusion from the ECS were:

- SOV2012-F1 subjects with major PDs in dosing meal at both breakfast and dinner at Visit 8 (Day 90).

Significant PDs leading to exclusion of the relevant 24-hour PK visit data only were:

- Not receiving any study drug on a 24-hour PK visit.
- Any use of Anabolic Steroid or Anti-androgens for more than 7 days or within 14 days before a 24-hour PK visit.
- Opioid, Spironolactone or oral ketoconazole use within 7 days before a 24-hour PK visit.
- SOV2012-F1 subject missing a 3 to 5 hour sample in combination with missing a 15 to 17 hour sample at confinement Visit 4, 6, or 8.
- AndroGel subject missing 2 samples out of the 2-hour, 4-hour and 8-hour samples at confinement Visit 8.
- Use of GI medications/protein pump inhibitors within 48 hours before a 24-hour PK visit did not exclude the relevant 24-hour PK visit data.

Confinement-visit specific PK concentration data from subjects within the PKS and/or ECS will be programmatically excluded from summary tables, summary figures, and statistical analyses if the subject did not receive any study drug prior to the planned sampling of the concentration profile.

Confinement-visit specific PK parameter data from subjects within the PKS and/or ECS will be programmatically excluded from summary tables, summary figures, and statistical analyses if the concentration profile was not evaluable per the outcome of the DRM or the subject did not receive any study drug prior to the planned sampling of the concentration profile.

No individual confinement-visit specific PK concentration or PK parameter data will be programmatically excluded from summary tables, summary figures, or statistical analyses for subjects within the FAS.

GI and urological surgery for SOV2012-F1 subjects were assessed on a case-by-case basis (whether having occurred prior to study entry or on study).

Prohibited natural supplements with hormonal effect did not exclude the subject from the PKS or ECS.

According to Quality Issue Summary Version 2.0[5] (regarding Site 141), the presence of extensive questions about source data, significant site compliance issues, and non-representative PK profiles for all four SOV2012-F1 subjects causes Marius to conclude that the PK data from this site are not valid. All Site 141 subjects (1411071, 1411092, 141951, and 141956) were excluded from the PKS and ECS. They were included in the SS and FAS where their PK data will be listed ,flagged, summarized and analyzed.

5.4.4. Significant Protocol Deviations: MRS-TU-2019EXT

Examples of significant PDs (but not limited to this list) leading to exclusion from the EXPK Set are:

- Taking prohibited 5 alpha-reductase inhibitors within one month before Visit 7E, or within six months before Visit 7E in the case of dutasteride.
- Meeting MRS-TU-2019 Exclusion Criterion 10 (relevant GI surgery).
- Not completing Visit 12E.
- Major PDs in dosing meal at both breakfast and dinner at Visit 12E.

Significant PDs leading to exclusion of the relevant 24-hour PK visit data only:

- Not receiving any study drug at Visit 12E.
- Any use of Anabolic Steroid or Anti-androgens for more than 7 days or within 14 days before Visit 12E.
- Opioid, Spironolactone or oral ketoconazole use within 7 days before Visit 12E.
- Missing a 3 to 5 hour sample in combination with missing a 15 to 17 hour sample at Visit 12E.

Visit 12E PK concentration data from subjects within the EXPK Set will be programmatically excluded from summary tables, summary figures, and statistical analyses if the subject did not receive any study drug prior to the planned sampling of the concentration profile.

Visit 12E PK parameter data from subjects within the EXPK Set will be programmatically excluded from summary tables, summary figures, and statistical analyses if the concentration profile is not evaluable per the outcome of the DRM or the subject did not receive any study drug prior to the planned sampling of the concentration profile.

GI and urological surgery will be assessed on a case-by-case basis (whether having occurred prior to MRS-TU-2019EXT study entry or on study).

These definitions will be discussed at the final DRM and therefore may be amended at that time.

5.4.5. Site 104

During study management it was noted that significant protocol deviations occurred at Study Site 104 during study MRS-TU-2019EXT resulting in exclusion of all subjects from the site for efficacy and C_{max} analysis. Two populations were created to exclude this site: mEXTS and mEXSE. The analysis set EXPK was also defined as excluding Site 104 subjects. Further details are described in Appendix 16.4.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.4 or higher.
Unless otherwise stated, summaries presented in tables will be presented by randomized or assigned treatment group. Any MRS-TU-2019 subjects receiving a treatment they were not randomized to, will be discussed in the CSR. Three subjects were randomized into the MRS-TU-2019 study twice in error and the handling of data for these subjects is described in Appendix 16.3.

Unless otherwise stated, summary statistics for continuous outcomes to be presented will include the number of non-missing observations (n), mean, SD, coefficient of variation (CV, %) calculated as 100%*SD/mean, median, minimum value, and maximum value. Unless otherwise stated, means and medians will be presented with one more decimal than the observed values. SD values will be presented with 2 more decimals than the observed values. CV values will be presented to 1 decimal place. Conventions for PK summaries are detailed separately in Section 9.4.2.

Categorical variables will be summarized using frequencies and percentages. Percentages will be calculated using the number of subjects in the analysis set or the number of subjects with a non-missing value for the assessment. The footnotes to the tables will note the method for calculating the percentages.

In general, subject listings will be provided for all data collected through MRS-TU-2019 and MRS-TU-2019EXT together. Exceptions will be for: subject disposition, where listings will be provided for screening and EOT separately for MRS-TU-2019 and MRS-TU-2019EXT. Listings for study drug administration, dose titration, exposure, and compliance, will be provided separately for MRS-TU-2019 SOV2012-F1 treatment arm, MRS-TU-2019 AndroGel treatment arm, and MRS-TU-2019EXT. For PK parameters and projected dose adjustments, listings will be provided separately for MRS-TU-2019 and MRS-TU-2019EXT. In general, listings will be sorted by subject identifier, date of collection, and time of collection (if applicable).

6.2. KEY DEFINITIONS

6.2.1. First Dose Date of Study Drug

The first dose date of study drug in MRS-TU-2019 will be defined as the date of the first a.m. dose on Visit 3 Day 1.

The first dose date of study drug in MRS-TU-2019EXT will be defined as the date of the first a.m. dose on Visit 7E Day 1E.

6.2.2. Last Dose Date of Study Drug

The last dose date of study drug in MRS-TU-2019 will be recorded at the Early Withdrawal or EOT visit.

The last dose date of study drug in MRS-TU-2019EXT will be recorded at Visit 16E EOT or at Early Withdrawal Visit E.

Missing and partial last dose dates will be handled according to Section 6.3.8.

6.2.3. Study Day

Study day for MRS-TU-2019 only subjects, and for MRS-TU-2019EXT continuing subjects and late entry subjects up to and including Visit 6E, will be calculated using the first dose date (Section 6.2.1) of MRS-TU-2019. For events/recordings of outcomes on or after the first dose date, the study day will be calculated as assessment date–first dose date+1. For events/recordings prior to the first dose date, the study day will be calculated as assessment date–first dose date. There will be no study Day 0.

Study day for MRS-TU-2019EXT will be calculated using the first dose date (Section 6.2.1) of MRS-TU-2019EXT. For events/recordings of outcomes on or after the first dose date, the study day will be calculated as assessment date–first dose date+1. For events/recordings prior to the first dose date, the study day will be calculated as assessment date–first dose date. There will be no study Day 0. In the tables, listings and figures (TLFs), study day will be displayed as xxxE.

6.2.4. Baseline

For MRS-TU-2019 subjects, baseline will be defined as the last non-missing observation prior to the first dose of study drug at Visit 3 (Day 1). For in-clinic BP for MRS-TU-2019, baseline will be defined as the within subject mean of all Screening Visit 2 and Visit 3 (Day 1) individual observations.

For MRS-TU-2019EXT subjects, baseline will be defined as the last non-missing observation prior to the first dose of study drug at Visit 7E (Day 1E). For in-clinic BP, baseline will be defined as the within subject mean of all Visit 6E individual observations. Baseline for ABPM statistic values will be the statistic value at Visit 7E (Day 1E). Baseline for hourly or half-hourly assessments will be time matched to the relative clock time at Visit 6E/7E.

6.2.5. Change from Baseline

Change from baseline = Post-baseline value – value at baseline.

6.2.6. Time 0 (Vital Signs)

For MRS-TU-2019, Time 0 is time of last recorded assessment(s) before morning dosing.

For MRS-TU-2019EXT ABPM visits, Time 0 is within 0.5 hour before placement of the ABPM cuff. For non-ABPM visits, Time 0 is the last recorded assessment(s) before the morning dose.

6.2.7. MRS-TU-2019 End of Treatment and Day 365 Visit

End of Treatment assessments, where subjects continue to take MRS-TU-2019 assigned treatment after study day 345 (≥345) will be assigned to the Day 365 visit, if the nominal Day 365 visit assessments are missing.

6.2.8. MRS-TU-2019EXT Enrolled

A subject is defined as enrolled into the MRS-TU-2019EXT study when they have provided informed consent and been deemed to have passed all MRS-TU-2019 and MRS-TU-2019EXT inclusion and exclusion criteria.

6.3. MISSING AND BELOW THE LIMIT OF QUANTIFICATION (BLQ) DATA

6.3.1. Missing ABPM Data

Only quality accepted ABPM readings will be included in calculations, summaries and analyses; criteria constituting a failed/rejected set of ABPM 24-hr data are defined as any of the following:

- More than 10 of the required 48 timepoints over 24 hours are missing/unreadable (>20%).
- More than 2 consecutive hours of data missing (5 or more consecutive 30-min data points missing).
- Less than 22 hours of recording time.

Only timepoints with both a baseline (Section 6.2.4) and a post baseline quality accepted reading will be evaluated for changes from baseline. Only timepoints with both a Day 120E and a Day 180E quality accepted reading will be evaluated for Day 180E changes from Day 120E.
No imputation methods will be employed.

6.3.2. Missing Data for Primary Endpoints

Following the parameter derivation of T C_{avg} according to Section 9.4.1, for the MRS-TU-2019 study, missing endpoint data will be imputed for the primary statistical analyses using a multiple imputation approach as detailed in Section 8.5 when at least one post baseline 24 hour T C_{avg} is evaluable.

For sensitivity analysis on the MRS-TU-2019 primary endpoint, worst-case scenario (WCS) imputations will be performed. Subjects with missing data at Visit 8 will be considered as treatment failures, i.e. they will be set to 24-hour T C_{avg} not within the normal range after 90 days of treatment. These analyses will be performed on the FAS.

For the primary analysis on the MRS-TU-2019EXT primary efficacy endpoint where there are no other post baseline C_{avg} values before Visit 12E (Day 90E), WCS imputations will be applied for the primary analysis. Subjects with missing data at Visit 12E will be considered as treatment failures, i.e. they will be set to 24-hour T C_{avg} not within the normal range after 90 days of treatment. This analysis will be performed on the mEXTS and EXTS.

6.3.3. Missing Pharmacokinetic (PK) Data

Missing PK concentration data will not be imputed for the purpose of calculating PK parameters for the particular subject and visit. However, if there is a missing sample collection time, the nominal (scheduled) sample collection time will be used based on a case-by-case review by the pharmacokineticist. If PK concentration data are missing, the pharmacokineticist will review on a case-by-case basis to determine if PK parameters should be calculated.

6.3.4. Below the Limit of Quantification (BLQ) PK Concentration Data

When handling PK concentration data that are BLQ, the following rules will apply for the derivation of PK parameters:

- BLQ concentration values for predose samples will be treated as zero.
- Postdose BLQ values prior to the first quantifiable concentration will be assigned as the predose concentration.
- Postdose BLQ values after the first quantifiable concentration will be treated as missing.

When handling PK concentration data that are BLQ, the following rules will apply for the calculation of summary statistics:

- BLQ concentration values for predose samples will be treated as zero.
- Postdose BLQ values prior to the first quantifiable concentration will be assigned as the predose concentration.
- Postdose BLQ values after the first quantifiable concentration will be treated as zero.

6.3.5. Missing Adverse Event (AE) Data

Imputation of AE onset, when a missing or partial onset date has been recorded, will be performed using the following algorithm, designed to conservatively assign AEs to a study period.

- If the onset date is entirely missing then the date of first dose of any study drug (Section 6.2.1) will be imputed as the onset date.

- If the year of onset only is provided and the year is the same as the year of first dose of any study drug, then the date of first dose (Section 6.2.1) will be imputed as the onset date. This event would be treatment-emergent. If the year of onset only is provided and the year is not the same as the year of first dose, then the onset date will be imputed as the 1st of January of that year.

- If only the month and year of onset are provided, and the month and year are equal to the month/ year of first dose of any study drug, then the date of first dose (Section 6.2.1) will be imputed as the onset date. In all other cases, the 1st day of the provided month/year of onset will imputed for the onset date. Only if the provided month/year of onset is prior to the month/year of first dose would an event **not** be considered treatment-emergent.

AEs with missing severity will be considered severe in the summaries.

TEAEs with missing relationship to study drug will be considered to be probably related to study drug in the summaries.

If a partial onset date is provided, the imputed onset date will be utilized for determination whether the event was treatment-emergent. Partial onset dates will be presented as reported by the investigator in the listings. Similarly, AEs with missing severity or relationship will be presented as missing in the listings.

If date of death is missing, date of last contact will be used.

6.3.6. Missing and Partial Medication Dates

In order to classify medications documented on the Prior and Concomitant Medications eCRF as prior or concomitant to a study or period, missing and partial medication dates will be handled as follows:

- Missing medication start dates likely to be after the date of first dose of study drug in MRS-TU-2019EXT (Section 6.2.1) will be imputed as the date of first dose of study drug in MRS-TU-2019EXT. Otherwise, missing medication start dates likely to be after the date of first dose of study drug in MRS-TU-2019 (Section 6.2.1) will be imputed as the date of first dose of study drug in MRS-TU-2019.

- Missing end dates will be imputed as the date of last contact.

- Incomplete medication start dates will be imputed using the earliest possible date implied by the portions of the date provided. If the year is provided and not the month (regardless of the day), January 1st of that year will be imputed as the start date. If the month and year are provided but not the day, the 1st day of the provided month/year will be imputed as the start date.

Incomplete medication end dates will be imputed using the latest possible date implied by the portions of the date provided. If only the year is provided and not the month regardless of the day, December 31st of that year will be imputed as the end date. If the month and year are provided but not the day, the last day of the provided month/year will be imputed as the end date. If any imputed end date would be after the subject's date of last contact, then the medication end date will be imputed as the date of last contact.

6.3.7. Missing and Partial Diagnosis Dates

In order to calculate the number of years since hypogonadism diagnosis, missing and partial diagnosis dates will be handled as follows:

Missing diagnosis dates will not be imputed.

Incomplete diagnosis dates will be imputed using the earliest possible date implied by the portions of the date provided. If only the year is provided and not month regardless of the day, January 1st of that year will be imputed as the start date. If the month and year are provided and not the day, the 1st day of the provided month/year will be imputed as the start date.

6.3.8. Missing and Partial Last Dose of Study Drug Dates

In order to calculate the duration of exposure of study drug, missing and partial last dose dates (Section 6.2.2) will be handled as follows:

Missing last dose dates will be imputed as the date of the last scheduled treatment visit.

Incomplete last dose dates will be imputed using the latest possible date implied by the portions of the date provided. If only the year is provided, December 31st of that year will be imputed as the last dose date. If the month and year are provided, the last day of the provided month/year will be imputed as the last dose date. If any imputed last dose date would be after the date of the subject's last scheduled treatment visit, then the last dose date will be imputed as the date of the last scheduled treatment visit.

6.4. VISIT WINDOWS

There are no plans to derive visit windows, visits will be used in the analyses as reported on the eCRF. For subjects with multiple screening attempts, only data from the most recent screening attempt will be included in summary statistics. Unscheduled PK and safety data (physical examination, vital signs, electrocardiogram [ECG], and laboratory evaluations) will not be summarized unless they are determined to be the last non-missing observations before the first dose of study drug (i.e. baseline [Section 6.2.4]). All data will be listed.

The T levels determined from the T assays processed at Syneos Health (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 T assay on the repeat PK samples will be considered the relevant T concentration.
PK samples taken far outside the protocol sampling window may be excluded from by-timepoint summary statistics; this will be decided by the pharmacokineticist.

6.5. POOLING OF CENTERS

No pooling of centers is planned. No listings, tables or analyses are planned to be presented by center.

6.6. SUBGROUPS

The MRS-TU-2019EXT analyses of C_{avg} and C_{max} will be presented separately for the following subgroups:

- Weight - ≤93 kg vs. >93 kg, as assessed at baseline (Section 6.2.4).
- BMI - <30 kg/m^2 vs. ≥30 kg/m^2, as assessed at Screening Visit 2.
- Age - ≤50 years vs. >50 years, as at date of informed consent.
- Race – Asian, Black or African American, White, or Other.
- Ethnicity.
- Actual Day 90E Breakfast Diet Category

For MRS-TU-2019, Time 0 (Section 6.2.6) vital signs summaries will be presented for the following subgroups, where applicable, as detailed in Section 16:

- Baseline Diabetic Status – with Diabetes Mellitus (baseline medical history of diabetes, or HbA1c at Visit 3 greater than 6.5%) and without Diabetes Mellitus.

- Baseline Hypertensive Status – hypertensive at baseline (baseline sBP ≥130 mmHg or dBP ≥80 mmHg) and not hypertensive at baseline.
- Baseline Hypertensive Treatment Status - with and without antihypertensive therapy at baseline, Visit 3 (Day 1).
- Day 90 Hemoglobin Tertiles. (Used for Day 90 In Clinic sBP)
- Baseline Hypogonadal Status:
    - Primary hypogonadism (LH and FSH above the upper limit of normal [ULN]).
    - Secondary hypogonadism where serum LH is within the normal range or below the lower limit of normal [LLN] and/or FSH is within the normal range or below the LLN).

For MRS-TU-2019EXT, Time 0 vital signs summaries will be presented for the following subgroups, where applicable, as detailed in Section 16:

- Baseline Diabetic Status – with Diabetes Mellitus (baseline medical history of diabetes, or HbA1c at Visit 7E greater than 6.5%) and without Diabetes Mellitus.
- Baseline Hypertensive Status – hypertensive at baseline (in clinic baseline sBP ≥130 mmHg or dBP ≥80 mmHg) and not hypertensive at in clinic baseline.
- Baseline Hypertensive Treatment Status - with and without antihypertensive therapy at baseline, Visit 7E (Day 1E).
- Baseline Hypogonadal Status:
    - Primary hypogonadism (LH and FSH above the upper limit of normal [ULN]).

Secondary hypogonadism where serum LH is within the normal range or below the lower limit of normal [LLN] and/or FSH is within the normal range or below the LLN).

- Baseline Statin Treatment Status – with and without statin treatment at baseline.
- Age - ≤50 years vs. >50 years, as at date of informed consent.

For the MRS-TU-2019EXT study, as data permit (minimum of 5 subjects per subgroup), subgroup analyses of 24-hour, daytime and nighttime ambulatory sBP and dBP, and 24-hour ambulatory HR, mean arterial pressure (MAP) and pulse pressure (PP), will be performed focusing on:

- Baseline Diabetic Status
- Baseline Hypertensive Treatment Status
- History of Hypertension
- Day 90E Hemoglobin Tertiles. (Used for Day 120E and Day 180E ABPM sBP)

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

7.1.1. MRS-TU-2019

The total number and percentage of subjects who screen failed will be summarized along with the number and percentage randomized to each treatment group, for all screened subjects.

The number and percentage of subjects within each analysis set and reasons for exclusion from each analysis set will be summarized by treatment group and overall in terms of the number of subjects randomized and/or treated.

Subject disposition will be summarized for all screened subjects and for the SS, FAS, PKS, ECS, and AAS by treatment group and overall. The summary table will show the frequency and percentage of subjects in each of the analysis sets who completed the study to Day 90, who completed the study to Day 365, who withdrew from the study before Day 90, who withdrew from the study between Day 90 and Day 365, and who withdrew from the study at any time before Day 365, along with the primary reason for discontinuation of study drug, with percentages based on the number of subjects randomized in the analysis set.

Reasons for discontinuation of study drug will also be listed, including the date of last dose of study drug (without imputation), date of last visit, and date of last follow-up.

Eligibility details (including date of screen failure and inclusion and/or exclusion criteria not met) and informed consent (protocol version, date informed consent signed, consent for ACTH sub-study, consent for BSSS, and consent for ABPM MRS-TU-2019EXT study) will be listed only, for all subjects screened.

Randomization details will also be listed, including the date of randomization and randomization number. Three subjects were randomized into the MRS-TU-2019 study twice in error and the handling of data for these subjects is described in Appendix 16.3.

7.1.2. MRS-TU-2019EXT

The number and percentage of subjects who screen failed, out of all those screened, will be summarized by source group (MRS-TU-2019 treatment group or newly enrolled group) and overall, for all screened subjects.

The number and percentage of subjects enrolled (Section 6.2.8), out of all those screened, overall and broken down by continuing subjects, late entry subjects who do not qualify as new enrollment subjects, and

newly enrolled subjects or late entry subjects who qualify for new enrollment, will be summarized by source group (MRS-TU-2019 treatment group or newly enrolled group) and overall, for all screened subjects.

The number and percentage of subjects within each analysis set and reasons for exclusion from each analysis set will be summarized in terms of the number of subjects providing written informed consent for the ABPM MRS-TU-2019EXT study.

Subject disposition will be summarized for all screened subjects, for all MRS-TU-2019EXT enrolled subjects (Section 6.2.8), and for the EXTS, mEXTS, EXPK Set and EXSE and mEXSE Set by source group (MRS-TU-2019 treatment group or newly enrolled group) and overall. The summary table will show the frequency and percentage of subjects in each of the analysis sets who enrolled (overall and broken down by continuing subjects, late entry subjects, and newly enrolled subjects), and who completed and withdrew from each relevant study period, along with the primary reason for discontinuation of study drug, with percentages based on the number of subjects enrolled in the analysis set. For MRS-TU-2019EXT the summary table will show the frequency and percentage of subjects who completed and withdrew from each relevant study period (to Day 90E, to Day 120E and to Day 180E). For MRS-TU-2019 the summary table will show the frequency and percentage of subjects who completed and withdrew from each relevant study period (to Day 90, to Day 365).

Reasons for discontinuation of study drug will also be listed, including the date of last dose of study drug (without imputation), date of last visit, and date of last follow-up.

Eligibility details (including date of screen failure and inclusion and/or exclusion criteria not met) for all screened subjects and informed consent date for all subjects providing written informed consent for the MRS-TU-2019EXT study will be listed only.

7.1.3. Overall

The number and percentage of subjects in the OSS and reasons for exclusion from the OSS will be summarized by source group (MRS-TU-2019 treatment group or MRS-TU-2019EXT newly enrolled group) and overall for all randomized or enrolled subjects and for all subjects who took SOV2012-F1 in both studies.

Subject disposition will be summarized for all subjects in the OSS and for all subjects who took SOV2012-F1 in both studies.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

All demography and baseline data will be listed.

Unless otherwise stated, percentages will be calculated out of the number of subjects in the analysis set. Three subjects were randomized into the MRS-TU-2019 study twice in error and the handling of data for these subjects is described in Appendix 16.3.

7.2.1. MRS-TU-2019

All demographic data will be summarized by treatment group and overall using descriptive statistics for the SS, FAS, PKS, ECS, and AAS.

Age (years) will be calculated as (date of informed consent-date of birth+1)/365.25 truncated to complete years and will be summarized as a continuous variable. Height and BMI are collected at Screening Visit 2 and will be summarized as continuous variables. BMI category at Screening Visit 2 (<30 kg/m^2 or ≥ 30 kg/m^2) will also be summarized by the number and percentage of subjects in each category. Diet category (low-, normal-, or high-fat breakfast) will be summarized by the number and percentage of subjects in each category using the Day 90 meal recorded in the CRF. The ASA 24 assigned diet category will also be summarized in the demography.

All remaining MRS-TU-2019 subgroup variables defined in Section 6.6 will be summarized by the number and percentage of subjects in each category.

Demography will also be broken down by the subgroups diabetic status and baseline hypertensive status as defined in Section 6.6.

7.2.2. MRS-TU-2019EXT

All demographic data will be summarized using descriptive statistics for the EXTS, mEXTS, EXPK, EXSE, and mEXSE.

Age (years) will be calculated as (date of MRS-TU-2019EXT informed consent-date of birth+1)/365.25 truncated to complete years and will be summarized as a continuous variable. Height and BMI are collected at Screening Visit 2 and will be summarized as continuous variables. BMI category at Screening Visit 2 (<30 kg/m^2 or ≥ 30 kg/m^2) will also be summarized by the number and percentage of subjects in each category. Diet category (low-, normal-, or high-fat breakfast) will be summarized by the number and percentage of subjects in each category using the Day 90E meal recorded in the CRF. The ASA 24 assigned diet category will also be summarized in the demography.

All remaining MRS-TU-2019EXT subgroup variables defined in Section 6.6 will be summarized by the number and percentage of subjects in each category.

7.2.3. Overall

All demographic data will be summarized using descriptive statistics for all subjects in the OSS and for all subjects who took SOV2012-F1 in both studies.

Age (years) will be calculated as (date of baseline informed consent-date of birth+1)/365.25 truncated to complete years and will be summarized as a continuous variable. Height and BMI are collected at Screening Visit 2 and will be summarized as continuous variables. BMI category at Screening Visit 2 (<30 kg/m^2 or ≥30 kg/m^2) will also be summarized by the number and percentage of subjects in each category.

7.3. BASELINE DISEASE CHARACTERISTICS

Symptoms and signs suggestive of androgen deficiency, present or past, are collected at Screening Visit 1 and will be summarized using descriptive statistics for categorical variables for the MRS-TU-2019 SS and the MRS-TU-2019EXT EXTS, and for all subjects in the OSS.

All data will be listed. Three subjects were randomized into the MRS-TU-2019 study twice in error and the handling of data for these subjects is described in Appendix 16.3.

7.4. MEDICAL HISTORY

Descriptions of medical history findings will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 or later. Details related to the subjects' hypogonadism will be specifically recorded. Medical/surgical history recorded at Screening Visit 1, will be summarized by the number and percentage of subjects within each SOC and PT, for the MRS-TU-2019 SS and the AAS by treatment group and overall; for the MRS-TU-2019EXT EXTS, mEXTS, EXPK, EXSE and mEXSE, and overall; for all subjects in the OSS; and for all subjects who took SOV2012-F1 in both studies. Subjects will be counted once per SOC and PT.

The number of years since hypogonadism diagnosis will be calculated as (date of informed consent – diagnosis date + 1)/365.25 for MRS-TU-2019, as (date of MRS-TU-2019EXT informed consent – diagnosis date + 1)/365.25 for MRS-TU-2019EXT, and as (date of baseline informed consent – diagnosis date + 1)/365.25 overall, and presented to 2 decimal places. Missing and partial diagnosis dates will be handled according to Section 6.3.7. The number of years since hypogonadism diagnosis will be summarized as a continuous variable for the MRS-TU-2019 SS, the FAS, the PKS, the ECS, and the AAS by treatment group and overall, for the EXTS, mEXTS EXPK Set, EXSE Set, and mEXSE Set overall, for all subjects in the OSS, and for all subjects who took SOV2012-F1 in both studies. Number and percentage of subjects with symptoms of hypogonadism and receiving prior TRT will also be summarized for the MRS-TU-2019 SS, the FAS, the PKS, the ECS, and the AAS by treatment group and overall, for the EXTS, mEXTS, EXPK, EXSE and mEXSE overall, for all subjects in the OSS, and for all subjects who took SOV2012-F1 in both studies.

Prior TRT recorded on the hypogonadism medical history eCRF will be coded using the World Health Organization (WHO) Drug B2 Format, 01MAR2017 version. The number and percentage of subjects receiving prior TRT as recorded at Screening Visit 1 will be summarized by ATC (Anatomical Therapeutic Chemical) Levels 2 and 4 for the MRT-TU-2019 SS, the FAS, the PKS, the ECS, and the AAS by treatment group and overall, for the EXTS, EXPK Set, and EXSE Set overall, for all subjects in the OSS, and for all subjects who took SOV2012-F1 in both studies. Subjects will be counted once per ATC class (Level 2) and PT (Level 4).

Medical history will also be listed for all subjects in the SS and the EXTS.

A disease or illness reported as medical history without a start date will be included in medical history without a date assigned.

Medical history will be sorted by descending overall frequency, by SOC and PT in the summary table. Medical history data listings will be sorted by treatment group, subject number, start date, SOC, PT, and verbatim term.

Three subjects were randomized into the MRS-TU-2019 study twice in error and the handling of data for these subjects is described in Appendix 16.3.

7.5. MEDICATION

Medications documented on the Prior and Concomitant Medications eCRF will be coded using the WHO Drug B2 Format, 01MAR2017 version. MRS-TU-2019 prior medications will be defined as medications documented on the Prior and Concomitant Medications eCRF that were started and stopped before the first dose of any study drug in MRS-TU-2019 (Section 6.2.1).

MRS-TU-2019EXT prior medications will be defined as medications documented on the Prior and Concomitant Medications eCRF that were started and stopped before the first dose of any study drug in MRS-TU-2019EXT (Section 6.2.1).

Overall prior medications will be defined as medications documented on the Prior and Concomitant Medications eCRF that were started and stopped before the first dose of any study drug for the subject (Section 6.2.1).

MRS-TU-2019 concomitant medications will be defined as medications documented on the Prior and Concomitant Medications eCRF that were started after the first dose of any study drug in MRS-TU-2019 (Section 6.2.1), and before the first dose of any study drug in MRS-TU-2019EXT (Section 6.2.1) for subjects taking part in MRS-TU-2019EXT, or started before the first dose of any study drug in MRS-TU-2019 and continued on or after the first dose of any study drug in MRS-TU-2019.

MRS-TU-2019EXT concomitant medications will be defined as medications documented on the Prior and Concomitant Medications eCRF that were started after the first dose of study drug in MRS-TU-2019EXT (Section 6.2.1) or started before the first dose of study drug in MRS-TU-2019EXT and continued on or after the first dose of study drug in MRS-TU-2019EXT. SOV2012-F1 concomitant medications will be defined as medications documented on the Prior and Concomitant Medications eCRF that were started after the first dose of SOV2012-F1 (Section 6.2.1) or started before the first dose of SOV2012-F1 and continued on or after the first dose of SOV2012-F1.

In order to classify medications documented on the Prior and Concomitant Medications eCRF as prior or concomitant to a study or period, missing and partial medication dates will be handled as detailed in Section 6.3.6.

The number and percentage of subjects taking MRS-TU-2019 prior medications will be summarized overall and by ATC Levels 2 and 4 for all subjects in the SS, the FAS, the PKS, the ECS, and the AAS by treatment group and overall. The number and percentage of subjects taking MRS-TU-2019EXT prior medications will be summarized overall and by ATC Levels 2 and 4 for all subjects in the EXTS, mEXTS, EXPK, EXSE, and mEXSE.

The number and percentage of subjects taking overall prior medications will be summarized overall and by ATC Levels 2 and 4 for all subjects in the OSS and for all subjects who took SOV2012-F1 in both studies.

The number and percentage of subjects taking MRS-TU-2019 concomitant medications will be summarized overall and by ATC Levels 2 and 4 for all subjects in the SS and AAS by treatment group and overall.

The number and percentage of subjects taking MRS-TU-2019EXT concomitant medications will be summarized overall and by ATC Levels 2 and 4 for all subjects in the EXTS, mEXTS, EXPK, EXSE, and mEXSE.

The number and percentage of subjects taking MRS-TU-2019EXT concomitant medications up to the Day 90E efficacy visit will be summarized overall and by ATC Levels 2 and 4 for all subjects in the EXTS, mEXTS, EXPK, EXSE, and mEXSE.

The number and percentage of subjects taking SOV2012-F1 concomitant medications will be summarized overall and by ATC Levels 2 and 4 for all subjects in the OSS and for all subjects who took SOV2012-F1 in both studies.

Subjects will be counted once per ATC class (Level 2) and PT (Level 4). Prior and concomitant medications will be listed together for all subjects in the SS and EXTS, with MRS-TU-2019EXT prior medications, MRS-TU-2019EXT concomitant medications started on or before the Day 90E visit, antihypertensive medications, and statin treatments being flagged. Prior TRT recorded on the hypogonadism medical history eCRF will be listed and summarized separately according to Section 7.4. The number and percentage of

subjects taking new antihypertensive therapy during the study that was not present at baseline, and the number and percentage of subjects with dose increases in antihypertensive therapy by EOT, will be summarized for the EXTS using summary statistics for categorical data.

Three subjects were randomized into the MRS-TU-2019 study twice in error and the handling of data for these subjects is described in Appendix 16.3.

8. EFFICACY

8.1. NORMAL RANGE

The T and DHT normal ranges for NaF/EDTA plasma and serum samples to be used in these studies in the evaluation of SOV2012-F1 treated subjects will be determined from Study MRS-TNR2019. The normal range for subjects treated with Androgel is 300 to 1000 ng/dL.

8.2. PRIMARY MRS-TU-2019 ENDPOINT

Three subjects were randomized into the study twice in error and the handling of data for these subjects is described in Appendix 16.3.

8.2.1. Multiple Imputation Analysis

Analysis of the primary endpoint will be performed using the FAS.

The primary endpoint is the percentage of SOV2012-F1–treated subjects with a 24-hour T C_{avg} (based on NaF/EDTA tube plasma samples) within the normal range after 90 days of treatment. The normal range is defined using the NaF/EDTA plasma endogenous testosterone from study MRS-TNR-2019.

The C_{avg} will be calculated per Section 9.4.1. Missing T C_{avg} values at Day 90 (Visit 8) in the FAS will be imputed using multiple imputation procedures, as described in Section 8.5. Multiple Imputation is only applied when there is at least one evaluable post baseline 24 hour T C_{avg}
A 95%, 2-sided, binomial CI for the percentage of subjects will be reported along with the estimated percentage itself. This CI will be calculated for each imputation generated from the multiple imputation procedure and results combined as described in Section 8.5.

Serum T C_{avg} values for those subjects randomly assigned to receive AndroGel will be summarized using summary statistics for continuous data only.

8.2.2. Sensitivity Analyses

Sensitivity Analysis 1 will be performed on SOV2012-F1-treated subjects using the ECS with no imputation of missing data.

Sensitivity Analysis 2 will be performed on SOV2012-F1-treated subjects using the FAS and WCS imputation, as described in Section 6.3.2.

8.3. PRIMARY MRS-TU-2019EXT EFFICACY ENDPOINT

8.3.1. Primary Analysis

The primary analysis of efficacy will be performed using the mEXTS.

The primary efficacy endpoint is the percentage of SOV2012-F1–treated subjects with a 24-hour plasma total T C_{avg} (based on NaF/EDTA tube plasma samples) within the normal range after 90 days of treatment within the MRS-TU-2019EXT study. The normal range is defined using the NaF/EDTA plasma endogenous testosterone from study MRS-TNR-2019.

The C_{avg} will be calculated per Section 9.4.1. Missing T C_{avg} values at Day 90E (Visit 12E) in the mEXTS will not be imputed using multiple imputation procedures, as there are no 24 hour pk profiles prior to Day 90E. Instead, missing values will be treated as failures (WCS).

A 95%, 2-sided, binomial CI (Wald asymptotic confidence limits) for the percentage of subjects will be reported along with the estimated percentage itself.

The MRS-TU-2019EXT study will have shown effectiveness of SOV2012-F1 if at least 75% of the mEXTS has total T C_{avg} in the normal range and if the lower bound of the 2-sided 95% CI for that proportion is ≥ 65%.

8.3.2. Sensitivity Analyses

The following sensitivity analyses will be performed:

- the EXTS and WCS imputation
- using the EXPK with no imputation of missing data.
- the mEXSE and WCS imputation using the serum and the NaF/EDTA plasma data from the Serum Substudy. The normal range is defined using the results from study MRS-TNR2019.
- the EXSE and WCS imputation using the serum and the NaF/EDTA plasma data from the Serum Substudy. The normal range is defined using the results from study MRS-TNR2019.

8.4. EXPLORATORY MRS-TU-2019 ENDPOINTS

Three subjects were randomized into the study twice in error and the handling of data for these subjects is described in Appendix 16.3.

8.4.1. International Prostate Symptom Score (I-PSS)

The I-PSS is a validated questionnaire used to assess the severity and impact of urinary symptoms. It is based on the answers to 7 questions concerning urinary symptoms and one question concerning quality of life. Each question concerning urinary symptoms allows the subject to choose one out of 6 answers indicating increasing severity of the particular symptom. The answers are assigned points from 0 to 5. The total score can therefore range from 0 to 35 (asymptomatic to very symptomatic).

The questions refer to the following urinary symptoms:

Questions	Symptom
1	Incomplete emptying
2	Frequency
3	Intermittency
4	Urgency
5	Weak Stream
6	Straining
7	Nocturia

Question 8 refers to the subject's perceived quality of life. The answers to the single quality of life question range from "delighted" to "terrible" or 0 to 6.

If any question response is left unanswered, then the resultant score will be missing and the total score will not be calculated.

The observed values and the change from baseline (Section 6.2.4) values for each subject will be summarized by treatment group and visit for total score and quality of life due to urinary symptoms score. Summaries will be completed separately for those who completed 52 weeks of treatment and those whose EOT assessment was completed at the time of early withdrawal, and for both groups together.

I-PSS summaries will be presented for the FAS. All questionnaire data will also be listed.

8.4.2. Psychosexual Daily Questionnaire (PDQ)

The PDQ will be used to assess the subject's sexual function and mood changes. Weekly averages of the PDQ subscale scores recorded for 7 consecutive days prior to the collection visit will be calculated. For the sexual activity subscale score, the weekly value will be sum of the number of "any" responses (1 = Yes, 0 = No), as detailed below. Scores are calculated if diaries are completed on at least 3 of the 7 consecutive days. The subscales are given below.

- Sexual desire
- Sexual enjoyment:
    - Enjoyment without a partner
    - Enjoyment with a partner
- Mood
    - Positive mood (Full of pep/energetic, Friendly, Well/good, and Alert)
    - Negative mood (Angry, Irritable, Sad or Blue, Tired, and Nervous)
- Sexual activity score
- Sexual performance with erection:
    - Percent full erection
    - Satisfaction with erection

The sexual desire subscale is assessed using a 0 – 7 Likert scale (None to Very High).

The sexual enjoyment with and without a partner subscales are assessed using a 0 – 7 Likert Scale (0 = None, 7 Very high enjoyment/pleasure). The availability of a partner (yes or no) is also recorded, but not used in the scoring.

The positive mood subscale score will be determined using each day's average response on the Likert Scale from 0 – 7 (0 = Not at all true – 7 = Very true) to the positive mood questions (alert, full of pep/energetic, friendly, well/good).

The negative mood subscale score will be determined using the same method as for the positive mood subscale score using the negative mood questions (angry, irritable, sad or blue, tired, nervous).

The weekly sexual activity subscale score will be determined using a count of the activities experienced over the complete assessment week, as indicated on the daily assessments (1 = experienced, 0 = did not experience), dividing by the number of days during the week where the daily questionnaire was completed, and then multiplying this ratio by 7 to get an activities per week value.

The percent of full erection is assessed by checking on the scale of 0 – 100% in increments of 10%.

Satisfaction with erection is assessed using a 0 – 7 Likert Scale (0 = not satisfactory – 7 = very satisfactory).

The observed and change from baseline (Section 6.2.4) weekly average values for each subject will be summarized by treatment group and visit for each subscale score. Summaries will be completed separately for those who completed 52 weeks of treatment and those whose EOT assessment was completed at the time of early withdrawal, and for both groups together.

PDQ summaries will be presented for the FAS. All questionnaire data will also be listed.

8.4.3. Short Form Survey (SF-36)

SF-36 is a set of generic, coherent, and easily administered quality-of-life measures. SF-36 will be scored according to the scorning manual for RAND 36-Item Health Survey (Version 1.0).".

Observed values and the change from baseline (Section 6.2.4) values for each subject will be summarized by treatment group and visit for each domain score, the physical (PCS) and mental (MCS) component summary scores, and the total score.

Summaries will be completed separately for those who completed 52 weeks of treatment and those whose EOT assessment was completed at the time of early withdrawal, and for both groups together.

SF-36 summaries will be presented for the FAS. All questionnaire data will also be listed.

8.4.4. International Index of Erectile Function Questionnaire (IIEF)

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. A score of 0-5 is awarded to the response given to each of the 15 questions that examine the 5 main domains of erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction, as detailed in Table 6.

Observed values and change from baseline (Section 6.2.4) values for each subject will be summarized by treatment group and visit for each totaled domain score. Note that the original Spanish version of the questionnaire used in the study had incorrect responses available for Question 12, therefore Question 12 was left blank in the eCRF for all subjects who used this version of the questionnaire. These data will not be imputed.

Summaries will be completed separately for those who completed 52 weeks of treatment and those whose EOT assessment was completed at the time of early withdrawal, and for both groups together.

IIEF summaries will be presented for the FAS. All questionnaire data will also be listed.

Table 6: Functional Domains and Numerical Responses for IIEF

Question Number on eCRF	Functional Domain	Categorical Response	Numerical Response
1	Erectile Function	No sexual activity	0
		Almost never or never	1
		A few times (much less than half the time)	2
		Sometimes (about half the time)	3
		Most times (much more than half the time)	4
		Almost always or always	5
2	Erectile Function	No sexual stimulation or intercourse	0
		Almost never or never	1
		A few times (much less than half the time)	2
		Sometimes (about half the time)	3
		Most times (much more than half the time)	4
		Almost always or always	5
3	Erectile Function	Did not attempt intercourse	0
		Almost never or never	1
		A few times (much less than half the time)	2
		Sometimes (about half the time)	3
		Most times (much more than half the time)	4
		Almost always or always	5
4	Erectile Function	Did not attempt intercourse	0
		Almost never or never	1
		A few times (much less than half the time)	2
		Sometimes (about half the time)	3

Question Number on eCRF	Functional Domain	Categorical Response	Numerical Response
		Most times (much more than half the time)	4
		Almost always or always	5
5	Erectile Function	Did not attempt intercourse	0
		Almost never or never	1
		A few times (much less than half the time)	2
		Sometimes (about half the time)	3
		Most times (much more than half the time)	4
		Almost always or always	5
6	Intercourse Satisfaction	No attempts	0
		1-2 attempts	1
		3-4 attempts	2
		5-6 attempts	3
		7-10 attempts	4
		11 or more attempts	5
7	Intercourse Satisfaction	Did not attempt intercourse	0
		Almost never or never	1
		A few times (much less than half the time)	2
		Sometimes (about half the time)	3
		Most times (much more than half the time)	4
		Almost always or always	5
8	Intercourse Satisfaction	No intercourse	0
		Not enjoyable	1
		Not very enjoyable	2
		Fairly enjoyable	3
		Highly enjoyable	4

Question Number on eCRF	Functional Domain	Categorical Response	Numerical Response
		Very highly enjoyable	5
9	Orgasmic Function	Did not attempt intercourse	0
		Almost never or never	1
		A few times (much less than half the time)	2
		Sometimes (about half the time)	3
		Most times (much more than half the time)	4
		Almost always or always	5
10	Orgasmic Function	No sexual stimulation or intercourse	0
		Almost never or never	1
		A few times (much less than half the time)	2
		Sometimes (about half the time)	3
		Most times (much more than half the time)	4
		Almost always or always	5
11	Sexual Desire	Almost never or never	1
		A few times (much less than half the time)	2
		Sometimes (about half the time)	3
		Most times (much more than half the time)	4
		Almost always or always	5
12	Sexual Desire	Very low or none at all	1
		Low	2
		Moderate	3
		High	4
		Very high	5
13	Overall Satisfaction	Very dissatisfied	1
		Moderately dissatisfied	2

Question Number on eCRF	Functional Domain	Categorical Response	Numerical Response
		About equally satisfied and dissatisfied	3
		Moderately satisfied	4
		Very satisfied	5
14	Overall Satisfaction	Very dissatisfied	1
		Moderately dissatisfied	2
		About equally satisfied and dissatisfied	3
		Moderately satisfied	4
		Very satisfied	5
15	Erectile Function	Very low	1
		Low	2
		Moderate	3
		High	4
		Very high	5

8.4.5. Fasting Serum Glucose and Fasting Insulin Concentrations

Fasting serum glucose is measured from the biochemistry blood samples taken at Screening Visit 2, Visits 4, 6, 8, 10, and 12, and EOT. Fasting insulin samples are taken at Visits 3, 4, 6, 8, 10, and 12, and Day 365.

The observed values and changes from baseline (Section 6.2.4) in fasting serum glucose and fasting insulin concentrations will be summarized for the SS by treatment group and visit.

8.5. MULTIPLE IMPUTATION METHODS

8.5.1. MRS-TU-2019 Imputation Procedure

Missing T C_{avg} values at Day 90 (Visit 8) will be imputed using a multiple imputation approach when there is at least one evaluable post baseline T C_{avg} prior to Day 90. If the subject has withdrawn from the study for any reason, missing values will be assumed to follow a distribution similar to values for subjects who

are still in the study and randomized to the same treatment group. Data will be imputed in 2 stages for SOV2012-F1 subjects.

Stage 1: Impute intermittent missing data for the SOV2012-F1 group
In a preliminary step, imputation based on the missing at random (MAR) assumption will be performed for intermittent missing data using the Markov chain Monte Carlo method in order to obtain monotone missing data patterns, and will be implemented with the SAS® PROC MI procedure with center, BMI at Screening Visit 2, age, race, and all visits with T C_{avg} data, included as terms in the imputation model. Race subgroups will be as defined in Section 6.6. Example SAS® code is as follows:

```
proc mi data=DATAIN nimpute=100 seed=543571857 out=MONOTONE;
var CENTER_X BMI AGE RACE_X VISIT4 VISIT6 VISIT8;
mcmc chain=multiple impute=monotone;
run;
```

where _X represents parameterized categorical variables.

Stage 2: Impute monotone missing data for the SOV2012-F1 group

1. Take the monotonic data set and create a new data set DATA1 including all subjects at Visit 4 with non-missing values or missing at Visit 4.
2. Sort by imputation (from the 100 imputations above) and subject number.
3. Impute data at Visit 4 in data set 1. Example SAS® code is as follows:

```
proc mi data=DATA1 out=VISIT4 seed=6784325 nimpute=1;
by _Imputation_;
class CENTER RACE;
var CENTER BMI AGE RACE VISIT4;
monotone regression;
run;
```

4. To impute missing data for the subsequent Visit 6 repeat steps 1 – 3 using the data set output above: VISIT4 instead of monotone, resulting in an output data set VISIT6.
5. Repeat for Visit 8.

For any visit, if there are no non-missing data for a center, then perform the above imputation once excluding the centers with no non-missing data at the visit, and once for the whole analysis set without center included in the model. From the second imputation, take the data for the centers that had no non-missing data at the visit and merge them back in with the data from the first imputation.

8.5.2. Analysis of Imputed Data

In order to analyze the data from the multiple imputation procedure the binomial CI at Day 90 will be calculated for each of the 100 imputations in Stage 2 above (Section 8.5.1, respectively), and then the results will be combined together to provide the final CI. This can be done as follows:

1. Calculate the binomial CI for each imputation.

```
PROC FREQ DATA=imputed_overall;
TABLES responder / cl binomial CL=wald;
BY _Imputation_;
ODS OUTPUT BINOMIAL=prop;
RUN;
```

2. Reformat the data.

```
DATA prop;
MERGE
prop(WHERE=(Label1=”Proportion”)
KEEP=_Imputation_ nValue1 Label1
RENAME=(nValue1=prop))
prop(WHERE=(Label1=”ASE”)
KEEP=_Imputation_ nValue1 Label1
RENAME=(nValue1=prop_se));
BY _Imputation_;
RUN;
```

3. Combine the results using PROC MIANALYZE

```
PROC MIANALYZE DATA=prop;
MODELEFFECTS prop;
STDERR prop_se;
ODS OUTPUT PARAMETERESTIMATES=mian_prop;
RUN;
```

9. ANALYSIS OF PHARMACOKINETICS (PK)

9.1. DATA SETS ANALYZED

The PKS and EXPK Set will be used for PK analyses. Three subjects were randomized into the MRS-TU-2019 study twice in error and the handling of data for these subjects is described in Appendix 16.3.

9.2. PHARMACOKINETIC (PK) SAMPLING SCHEDULE

The time of dosing and each blood sampling will be recorded to the minute according to nominal scheduled timepoints listed in Table 7 and Table 8.

Table 7: Scheduled Nominal Timepoints for SOV2012-F1 PK Blood Samples

Study Visit/Day	Specimens	Analytes	Plasma Tubes	Blood Samples Assay Timepoints
Visit 3/Day 1	Plasma	T, DHT, E2	NaF/EDTA	Pre-morning dose
Visit 4/Day 14	Plasma	T, DHT	NaF/EDTA	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	Plasma	T, DHT	NaF/EDTA	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 8/Day 90	Plasma	TU, DHTU, T, DHT E2	NaF/EDTA EDTA	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 9/Day 166	Plasma	T, DHT	NaF/EDTA	3-5 hours after a.m. dose
Visit 11/Day 256	Plasma	T, DHT	NaF/EDTA	3-5 hours after a.m. dose
Visit 13/Day 365	Plasma	T, DHT	NaF/EDTA	3-5 hours after a.m. dose
Visit 7E/Day 1E	Plasma and Serum	T, DHT	EDTA and NaF/EDTA	Pre-morning dose
	Plasma	E2	EDTA	Pre-morning dose
Visit 8E/Day 14E	Plasma and Serum	T, DHT	EDTA and NaF/EDTA	Pre-morning dose and 1.5, 3, 4, 5, 6
Visit 10E/Day 42E	Plasma and Serum	T, DHT	EDTA and NaF/EDTA	Pre-morning dose and 1.5, 3, 4, 5, 6

Visit 12E/Day 90E	Plasma	TU, DHTU E2	NaF/EDTA EDTA	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
	Plasma and Serum[a]	T, DHT	EDTA and NaF/EDTA	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

[a] Serum samples obtained for approximately 100 subjects in MRS-TU-2019EXT at Visit 12E.

Unless otherwise stated, summaries and analyses for the MRS-TU-2019EXT study will use the plasma samples from the NaF/EDTA tubes (E2 uses EDTA tubes).

Table 8: Scheduled Nominal Timepoints for AndroGel PK 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

9.3. PHARMACOKINETIC (PK) CONCENTRATION DATA

9.3.1. Handling of Missing Data and Data Below the Limit of Quantification (BLQ)

Missing PK concentrations and sample collection times will be handled according to Section 6.3.3. BLQ PK concentration data will be handled according to Section 6.3.4.

9.3.2. Presentation of Pharmacokinetic (PK) Concentration Data

The following presentations of subject concentration data will be provided for each analyte, unless otherwise specified, for the PKS or EXPK Set using nominal times. For mean ± SD plots, lower SD bars will be truncated at 0.

- Listing including subject, timepoint (actual, planned, deviation time) and treatment (including 24-hour PK timepoints and other single timepoints) for the SS or EXTS. No imputed data will be included in the data listings.

- MRS-TU-2019 individual subject linear plasma T concentration-time plots by Day (24-hour PK only) for SOV2012-F1-treated subjects.
- MRS-TU-2019 individual subject linear serum T concentration-time plots at Day 90 for AndroGel-treated subjects.
- MRS-TU-2019EXT individual subject linear plasma and serum T concentration-time plots by Day (6-hour and 24-hour PK only).
- MRS-TU-2019EXT individual subject linear TU concentration-time plots at Day 90E.
- Summary of MRS-TU-2019 concentration by treatment group at each timepoint (including 24-hour PK timepoints and other single timepoints) (n, number of values below BLQ [nBLQ], mean, SD, CV, minimum, median, maximum, geometric mean, and geometric CV).
- Summary of MRS-TU-2019EXT concentration at each timepoint (including 24-hour PK timepoints and other single timepoints) (n, nBLQ, mean, SD, CV, minimum, median, maximum, geometric mean, and geometric CV).
- Summary of MRS-TU-2019 T, DHT, and E2 concentration by dose by treatment group at each timepoint by Day (24-hour PK only) (n, nBLQ, mean, SD, CV, minimum, median, maximum, geometric mean, and geometric CV).
- Summary of MRS-TU-2019EXT T, DHT, and E2 concentration by dose at each timepoint by Day (6-hour and 24-hour PK only) (n, nBLQ, mean, SD, CV, minimum, median, maximum, geometric mean, and geometric CV).
- MRS-TU-2019 mean ± SD concentration-time profiles by treatment group by Day (24-hour PK only) on a linear scale.
- MRS-TU-2019 mean + SD concentration-time profiles by treatment group by Day (24-hour PK only) on a log-linear scale.
- MRS-TU-2019EXT mean ± SD concentration-time profiles by Day (6-hour and 24-hour PK only) on a linear scale.
- MRS-TU-2019EXT mean + SD concentration-time profiles by Day (6-hour and 24-hour PK only) on a log-linear scale.

- MRS-TU-2019EXT mean ± SD concentration-time profiles at Day 90E on a linear scale.
- MRS-TU-2019EXT mean + SD concentration-time profiles at Day 90E on a log-linear scale.
- MRS-TU-2019 mean ± SD T and DHT concentration-time profiles by dose by treatment group by Day (24-hour PK only) on a linear scale.
- MRS-TU-2019 mean + SD T and DHT concentration-time profiles by dose by treatment group by Day (24-hour PK only) on a log-linear scale.
- MRS-TU-2019EXT mean ± SD T and DHT concentration-time profiles by dose by Day (6-hour and 24-hour PK only) on a linear scale.
- MRS-TU-2019EXT mean + SD T and DHT concentration-time profiles by dose by Day (6-hour and 24-hour PK only) on a log-linear scale.
- Mean ± SD T concentration-time profiles for pre-morning dose at Days 1, 14, 42, and 90 by treatment group on a linear scale.
- Mean ± SD T concentration-time profiles for pre-morning dose at Days 1E, 14E, 42E, and 90E on a linear scale.
- Mean ± SD T concentration-time profiles (12-hour PK on Day 90 and Day 90E only) by diet categories as determined by the breakfast meal received on that day (low-, normal-, or high-fat) on a linear scale for SOV2012-F1-treated subjects.
- Mean ± SD T concentration-time profiles (12-24 hour PK on Day 90 and Day 90E only) by dinner fat categories as determined by the evening meal received on that day (low-, normal-, or high-fat) on a linear scale for SOV2012-F1-treated subjects.

ASA24 system record and SOV2012-F1 on-site meal record details will be listed.

Reporting precision for summaries of subject concentration data will be the same as that for the PK Parameters in Section 9.4.2.

9.4. PHARMACOKINETIC (PK) PARAMETERS

9.4.1. Derivation of Pharmacokinetic (PK) Parameters

Validated WinNonLin Version 6.4 (Certara, USA) will be used for PK parameter derivation. PK parameters detailed in Section 4.3 will be estimated using the concentrations with rules for BLQ and missing data (as detailed in Section 9.3.1) applied. The sampling time relative to dosing for predose samples will be treated as zero. Further details of PK parameter derivation (24-hour PK sampling only) are as follows:

- The C_{max} and the corresponding T_{max} will be read directly from the concentration-time plot (observed data, not predicted data, excluding the pre-morning dose data). If the same C_{max} is recorded more than once during the treatment period, the earliest occurrence will be considered the T_{max}.
- AUCs will be calculated non-compartmentally using the linear up/log down trapezoidal rule.
- The C_{avg} will be calculated as AUC_{0-24} divided by 24 hours. If AUC_{0-24} is not calculable, and the last timepoint (T_{last}) is close to 24 hours (between 23 and 25 hours inclusive), then $C_{avg0-last}$ calculated as AUC_{last}/T_{last} will be used for C_{avg}.
- DHT/T and E2/T ratios will be calculated based on ratios of C_{avg}, AUC_{0-12}, and AUC_{12-24} normalized by molecular weight using following equations:

  1) DHT/T C_{avg} = [(DHT C_{avg})*FW_T]/[(T C_{avg})*FW_{DHT}]

  2) E2/T C_{avg} = [(E2 C_{avg})*FW_T]/[(T C_{avg})*FW_{E2}]

  Where FW_T = 288.42 g/mol; FW_{DHT} = 290.44 g/mol; FW_{E2} = 272.38 g/mol

  The same equations will be applied with the other parameters in replacement of C_{avg} for AUC_{0-12}, and AUC_{12-24} based ratios.

Free T concentrations at MRS-TU-2019 baseline (Section 6.2.4), MRS-TU-2019EXT baseline, and for Day 90 and Day 90E will be calculated using total T (pre-dose for Visit 3 and 7E, and C_{avg} from Day 90 and Day 90E), SHBG, and albumin concentrations for each subject according to a validated FTV method[6,7] with the following equation:

$FTV = (T–N*FTV)/(K_t(S–T+N*FTV))$

FTV is then converted to ng/dL by multiplying by 28.842

Where FTV = free T concentration (nmol/L), T = total T concentration (nmol/L), S = SHBG concentration (nmol/L), K_t = (association constant of SHBG for T) = 0.597 L/nmol, N = (K_aC_a+1), $K_a = 3.6*10^4$ L/mol, C_a = albumin molar concentration (mol/L), and 28.842 is the conversion factor of nmol/L to ng/dL

For albumin, molar concentration conversion will be:

albumin concentration (g/L) divided by 69000 (g/mol) = xx (mol/L).

Free T calculations will be performed using Total T (pre-dose for Visit 3 and 7E, and C_{avg} from Day 90 and Day 90E) from NaF/EDTA samples for MRS-TU-2019 and MRS-TU-2019EXT for the SOV2012-F1 treatment groups and from the serum samples for the AndroGel treatment group. Free T calculations will also be performed for both serum and NaF/EDTA samples from the MRS-TU-2019EXT Serum Substudy.

9.4.2. Presentation of Pharmacokinetic (PK) Parameters

Individual subject PK parameters will be listed for each analyte.

PK parameters will be summarized by treatment group for the PKS and summarized for the EXPK Set using descriptive statistics as detailed in Table 9.

The following tables will be provided for the PKS and EXPK Set using descriptive statistics as detailed in Table 9:

- Plasma 0-24, and 0-12 T C_{avg} and T C_{max} on Day 90E by diet category as determined by the meal received on that day (low-, normal-, or high-fat breakfast) and overall.
- Plasma 12-24 T C_{avg} and T C_{max} on Day 90E by diet category as determined by the meal received on that day (low-, normal-, or high-fat dinner).
- Plasma 0-24, and 0-12 T C_{avg} and T C_{max} on Day 90 by diet category as determined by the meal received on that day (low-, normal-, or high-fat breakfast) and overall.
- Plasma 12-24 T C_{avg} and T C_{max} on Day 90 by diet category as determined by the meal received on that day (low-, normal-, or high-fat dinner).
- Plasma 0-24 T C_{avg} and T C_{max} on Day 90E by the subgroups detailed in Section 6.6 and overall.

Table 9: PK Parameters – Summary Statistics

Variable	Summarized with:
AUC, C_{max}, C_{avg} for 0-12, 0-24 and 12-24	n, arithmetic mean, SD, CV (%) calculated as 100%*SD/mean, minimum, first quartile (Q1), median, third quartile (Q3), maximum, geometric mean, and geometric CV, calculated as Geometric CV (%) = $100\% * \sqrt{e^{z^2} - 1}$, where z^2 is the variance of $\ln(x_i)$
DHT/T and E2/T ratios	n, arithmetic mean, SD, CV, minimum, Q1, median, Q3, maximum
Free T	n, arithmetic mean, SD, CV, minimum, median, maximum
T_{max}, T_{last}	n, minimum, median, and maximum

The conventions to be used for the presentation of the descriptive statistics of PK parameters and concentrations are detailed in Table 10.

Table 10: PK Parameters – Reporting Precision

Statistics	Degree of Precision
Minimum, Q1, Median, Q3, Maximum	3 significant digits
Mean (arithmetic and geometric)	3 significant digits
SD	3 significant digits
CV and Geometric CV	1 decimal place

The number and percentage of subjects with plasma DHT C_{avg} and DHT C_{max} greater than 1, 2, 3, and 5 times the ULN on Day 90E in the EXPK Set will be presented. The DHT normal range is defined in Section 8.1.

The following graphic presentations will be provided for the SOV2012-F1-treated subjects in the PKS or the EXPK:

- Histograms of plasma T C_{avg} and T C_{max} respectively (24-hour PK on Day 90 and Day 90E only) on a linear scale.

- Box plots of plasma T C_{avg} and T C_{max} respectively (0-12 and 12-24-hour PK on Day 90E only) by diet categories (low-, normal-, or high-fat dinner or breakfast) as determined by the meal received on that day on a linear scale.

- Box plots of plasma T C_{avg} and T C_{max} respectively (24-hour PK on Day 90E only) by the subgroups detailed in Section 6.6 on a linear scale.

9.5. MRS-TU-2019 SOV2012-F1 TITRATION ALGORITHM EVALUATION

An evaluation of the MRS-TU-2019 titration algorithm was performed at the interim analysis and the methods were detailed in Version 2.0 of this SAP. The evaluation is reported in Appendix 16.2 and was used to determine the titration algorithm for MRS-TU-2019EXT.

9.6. MRS-TU-2019EXT SOV2012-F1 TITRATION ALGORITHM EVALUATION FOR SAMPLING TIME AND MATRIX EFFECTS

9.6.1. Analysis of T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E) vs. Visit 10E (Day 42E) Titration Time,

The number and percentage of subjects with a 24-hour plasma total T C_{avg} for NaF/EDTA plasma and serum for the EXSE and mEXSE within and outside the normal range after 90 days of treatment within the MRS-TU-2019EXT study will be presented by the Visit 10E timepoint that was used to determine the need, if any, to up or down titrate the dose of SOV2012-F1.

9.6.2. Plasma Projected Dose Adjustments

In order to make the claim that the window of the timepoints that were used to determine the need, if any, to up or down titrate the dose of SOV2012-F1 (3, 4, and 5 hours) using plasma T concentration, an analysis of projected dose adjustment (increase, decrease, or no change) at 3, 4, 5 and 6 hours at Visits 8E (Day 14E) and 10E (Day 42E) will be performed. Each hour will be compared to the other hours to see if the decision to dose adjust is the same. The percentage and frequency of matches will be presented.

9.6.3. Actual and Projected Titration Decisions

For titration visits in MRS-TU-2019EXT ,plasma actual titration decisions and serum projected titration decisions (increase, decrease, no change) will be summarized by assessment hour (3, 4, and 5). Serum projections will be programmatically determined using the range of 460 to 971 ng/dL

Plasma titration decisions are actual decision during clinical conduct using plasma titration thresholds of 400 and 900 ng/dL.

9.6.4. Spearman's Correlation Matrix of Projected Dose Adjustments

For each of Visit 8E (Day 14E) and Visit 10E (Day 42E) and each timepoint (1.5, 3, 4, 5, and 6 hours), a Spearman's correlation matrix of projected dose adjustment (increase, decrease, or no change) will be presented for both NaF/EDTA plasma and serum.

9.6.5. Adjustment of NaF/EDTA Titration Thresholds to Serum Basis

Using the EXPK Set, the relationship between serum T concentrations and plasma T concentrations using NaF/EDTA tubes will be evaluated for each of the titration visits (8E and 10E), at the 3, 4, 5, and 6 hour timepoints separately, through scatter plots. A simple regression line will be displayed on each plot with the estimate of the slope and the 95% CI and p-value for the estimate of the slope, along with the adjusted R-squared. Then hours combined for 3,4,5 and then hours combined for 4,5,6 and finally all hours combined combined will also be presented with regression line, adjusted R-squared, and slope estimates.

9.6.6. Final Dose as an Outcome Variable

With baseline hypertensive status, diabetes, and baseline weight as factors a logistic regression will be performed to assess the relationship to final dose in the EXTS set. Dose will fall into one of the following three categories: 800mg, 600mg, and ≤400mg. Odds ratios and 95% CIs will be provided for each of the factors.

9.7. ANALYSIS OF FOOD EFFECT

For the following parameters (Cavg0-24, Cmax0-24, Cavg0-12, Cmax0-12, Cavg12-24, and Cmax12-24) in both MRS-TU-2019 and MRS-TU-2019EXT, a food effect analysis will be performed comparing low and high fat meals to normal fat(reference). Parameters will be natural log transformed prior to analysis. The difference in geometric least squares means and associated 90% confidence intervals will be back transformed to provide the ratio and associated 90% confidence interval.

10. SAFETY

General safety endpoints are detailed in Sections 4.1.4 and 4.2.3. General safety will be assessed on the basis of AE reports, clinical laboratory data, vital signs, and serum cortisol response to intravenous administration of synthetic ACTH. Other safety assessments are physical examinations and ECG. The SS will be used for all general MRS-TU-2019 safety analyses, except the ACTH analysis, which will be performed using the AAS. The EXTS will be used for all general MRS-TU-2019EXT safety analyses. The OSS will be used for overall safety analyses.

The safety objectives are to assess the safety data after 52 weeks of treatment in the MRS-TU-2019 study and after 180 days of treatment in the MRS-TU-2019EXT study; however, selected safety data were also presented at the Day 90 interim analysis as detailed in Version 2.0 of this SAP.

Vital signs will also be evaluated using ABPM. The primary ABPM endpoint is the change from baseline in 24-hour average ambulatory sBP after approximately 120 (±3) days of treatment in the MRS-TU-2019EXT study and will be analyzed using the EXTS.

Also part of the safety evaluations, T C_{max} after 90 days of treatment in the MRS-TU-2019 study will be analyzed using the FAS. Other safety endpoints for the MRS-TU-2019EXT study are detailed in Section 4.2.2 and will be analyzed using the EXTS.

Three subjects were randomized into the MRS-TU-2019 study twice in error and the handling of data for these subjects is described in Appendix 16.3.

10.1. EXTENT OF EXPOSURE

Shift tables from dose level at the start of each scheduled dose adjustment visit to dose level at the end of the visit (i.e. after dose adjustment) will be presented by treatment group for MRS-TU-2019 and separately for MRS-TU-2019EXT. The final study drug dose level at the end of every scheduled study visit will also be summarized by treatment group for MRS-TU-2019 and separately for MRS-TU-2019EXT. Percentages will be calculated out of the number of subjects attending the visit.

Categorical summaries of number of titrations and final study drug dose level reached will be presented for MRS-TU-2019 by treatment received, and for MRS-TU-2019EXT overall.

Bar charts of the number of subjects at each dose at Visit 4 (Day 14), Visit 6 (Day 42), Visit 8 (Day 90) and Visit 8E (Day 14E), Visit 10E (Day 42E) and Visit 12E (Day 90E) will be presented by treatment group for MRS-TU-2019 and separately for MRS-TU-2019EXT.

Summary statistics of the average dose daily dose at Visit 4, Visit 6 and Visit 8 (Day 90) for MRS-TU-2019 , and also for Visit 8E, Visit 10E and Visit 12E MRS-TU-2019EXT will be calculated.

Duration of exposure to study drug in days will be summarized for MRS-TU-2019 by treatment received, for MRS-TU-2019EXT overall, and for SOV2012-F1 overall for all subjects in the OSS and for all subjects who took SOV2012-F1 in both studies, and will be calculated as follows, where missing and partial last study drug administration dates will be handled according to Section 6.3.8:

- For MRS-TU-2019, duration of exposure (days) = (last date study drug administration in MRS-TU-2019–first date study drug administration in MRS-TU-2019 +1).

- For MRS-TU-2019EXT, duration of exposure (days) = (last date study drug administration in MRS-TU-2019EXT–first date study drug administration in MRS-TU-2019EXT +1).

- For SOV2012-F1 overall for all subjects in the OSS, duration of exposure (days) = (last date SOV2012-F1 administration in MRS-TU-2019–first date SOV2012-F1 administration in MRS-TU-2019 +1)+(last date SOV2012-F1 administration in MRS-TU-2019EXT–first date SOV2012-F1 administration in MRS-TU-2019EXT +1).

- For all subjects who took SOV2012-F1 in both studies, duration of exposure (days) is the sum of exposure in MRS-TU-2019 and MRS-TU-2019EXT. .

Cumulative total dosage consumed will be summarized for MRS-TU-2019 by treatment received, for MRS-TU-2019EXT overall, and for SOV2012-F1 overall for all subjects in the OSS and for all subjects who took SOV2012-F1 in both studies, and will be calculated as follows:

- For AndroGel-treated subjects, total dose consumed (g) = sum of (dispensed weight (g)-returned weight (g) for each bottle dispensed).

- For SOV2012-F1-treated subjects in MRS-TU-2019, total dose consumed in MRS-TU-2019 will be calculated 2 ways:

    1) Total dose consumed (g) = 0.2 g*total number of capsules reported as taken or missing in MRS-TU-2019.

    2) Total dose consumed (g) = 0.2 g*total number of capsules reported as taken in MRS-TU-2019.

  Where missing capsules are the total number of capsules not returned minus the number of capsules reported as taken.

- For MRS-TU-2019EXT, total dose consumed in MRS-TU-2019EXT will be calculated 2 ways:

1) Total dose consumed (g) = 0.1 g*total number of 100 mg capsules reported as taken or missing in MRS-TU-2019EXT+0.15 g*total number of 150 mg capsules reported as taken or missing in MRS-TU-2019EXT+0.2 g*total number of 200 mg capsules reported as taken or missing in MRS-TU-2019EXT.

2) Total dose consumed (g) = 0.1 g*total number of 100 mg capsules reported as taken in MRS-TU-2019EXT+0.15 g*total number of 150 mg capsules reported as taken in MRS-TU-2019EXT+0.2 g*total number of 200 mg capsules reported as taken in MRS-TU-2019EXT.

- For all subjects in the OSS, total dose of SOV2012-F1 consumed overall will be calculated 2 ways:

1) Total dose consumed (g) = 0.2 g*total number of capsules reported as taken or missing in MRS-TU-2019+0.1 g*total number of 100 mg capsules reported as taken or missing in MRS-TU-2019EXT+0.15 g*total number of 150 mg capsules reported as taken or missing in MRS-TU-2019EXT+0.2 g*total number of 200 mg capsules reported as taken or missing in MRS-TU-2019EXT.

2) Total dose consumed (g) = 0.2 g*total number of capsules reported as taken in MRS-TU-2019+0.1 g*total number of 100 mg capsules reported as taken in MRS-TU-2019EXT+0.15 g*total number of 150 mg capsules reported as taken in MRS-TU-2019EXT+0.2 g*total number of 200 mg capsules reported as taken in MRS-TU-2019EXT.

All data will be listed. Three subjects were randomized into the MRS-TU-2019 study twice in error and the handling of data for these subjects is described in Appendix 16.3.

10.2. TREATMENT COMPLIANCE

Subject compliance with the dosing regimen will be assessed at Visit 5 (Day 28), Visit 7 (Day 56), Visit 8 (Day 90), Visit 10 (Day 180), Visit 12 (Day 270), EOT, Visit 9E (Day 28E), Visit 11E (Day 56E), Visit 12E (Day 90E), Visit 14E (Day 120E), Visit 16E (Day 180E), and Early Withdrawal Visit E.

Study drug compliance (%) will be calculated for each of these dosing compliance periods attended as 100*the actual dose consumed divided by the expected dose, where:

- For SOV2012-F1-treated subjects, actual dose consumed will be calculated 2 ways:

1) Actual dose consumed = 0.1 g*number of 100 mg capsules reported as taken or missing+0.15 g*number of 150 mg capsules reported as taken or missing+0.2 g*number

of 200 mg capsules reported as taken or missing, i.e. assuming missing capsules were taken.

2) Actual dose consumed = 0.1 g*number of 100 mg capsules reported as taken+0.15 g*number of 150 mg capsules reported as taken+0.2 g*number of 200 mg capsules reported as taken, i.e. assuming missing capsules were not taken.

- For AndroGel-treated subjects, actual dose consumed = 0.0162*(dispensed weight (g)-returned weight (g)).

- Expected dose = scheduled number of days between compliance assessment visits*assigned dose level (g).

Overall study drug compliance (%) will be calculated separately for the MRS-TU-2019 study and the MRS-TU-2019EXT study and overall for SOV2012-F1 as 100*the overall actual dose consumed in the study divided by the overall expected dose for the study, where:

- Overall Actual Dose Consumed in the study = sum of actual dose consumed for each dosing compliance period attended in the study.

- Overall Expected Dose for the study = sum of Expected Dose for each dosing compliance period attended in the study.

Study drug compliance to Day 90 (%) will be calculated as 100*the actual dose consumed to Day 90 divided by the expected dose to Day 90, where:

- Actual Dose Consumed to Day 90 = sum of actual dose consumed for each dosing compliance period attended between Visits 3 and 8.

- Expected Dose to Day 90 = 28*assigned dose level (g) for Visit 3 to Visit 5 dosing compliance period+28*assigned dose level (g) for Visit 5 to Visit 7 dosing compliance period+34*assigned dose level (g) for Visit 7 to Visit 8 dosing compliance period.

MRS-TU-2019EXT Study drug compliance to Day 90E (%) will be calculated as 100*the actual dose consumed between Day 1E and Day 90E divided by the expected dose between Day 1E and Day 90E, where:

- Actual Dose Consumed to Day 90E = sum of actual dose consumed for each dosing compliance period attended between Visits 7E and 12E.

- Expected Dose to Day 90E = 28*assigned dose level (g) for Visit 7E to Visit 9E dosing compliance period+28*assigned dose level (g) for Visit 9E to Visit 11E dosing compliance period+34*assigned dose level (g) for Visit 11E to Visit 12E dosing compliance period.

Overall MRS-TU-2019 study drug compliance and study drug compliance to Day 90 will be summarized for the SS, FAS, PKS, ECS, and AAS by treatment group using summary statistics for continuous data. Overall MRS-TU-2019EXT study drug compliance and study drug compliance to Day 90E will be summarized for the EXTS, mEXTS, EXSE and mEXSE and the EXPK using summary statistics for continuous data. Overall SOV2012-F1 compliance will be summarized for all subjects in the OSS and for all subjects who took SOV2012-F1 in both studies using summary statistics for continuous data. The number and percentage of subjects in each of the following categories of compliance for each of these periods and analysis sets will also be presented:

- <80%.
- 80% to 120%.
- >120%.

All calculated compliance data will be listed.

10.3. AMBULATORY BLOOD PRESSURE MONITORING (ABPM)

ABPM analyses will be performed using the EXTS.

Missing data will be handled as described in Section 6.3.1.

10.3.1. 24-hour Average Ambulatory sBP

The 24-hour average ambulatory sBP and changes from baseline (Section 6.2.4) will be summarized by visit using summary statistics for continuous variables, including 95% CIs for the means.

To evaluate central tendency and outliers, a box plot of 24-hour average ambulatory sBP will be presented overlaying visit. A cumulative distribution curve of 24-hour average ambulatory sBP will be presented overlaying visit.

In addition, a mixed model repeated measures analysis on the 24-hour average ambulatory sBP will be performed with subject as a random effect (all subjects with non-missing post-baseline results), and visit (7E, 14E and 16E), MRS-TU-2019 prior randomized treatment (SOV2012-F1, AndroGel, or None for MRS-TU-2019 naïve subjects), and baseline hypertensive treatment status as fixed effects. Additional

effects such as baseline diabetic status (Section 6.6) will be considered for inclusion. An unstructured covariance structure will be used to model the within-subject errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The least squares mean at each visit and the least squares mean for the difference between Day 120E and Day 1E with the associated 95% CIs will be provided. Goodness of fit will be evaluated. A sensitivity analysis will be performed only including subjects with non-missing results at all of Visits 7E, 14E and 16E (ABPM completers).
24-hour average change from baseline ambulatory sBP values will be categorized into 5 mmHg increments to ±20 mmHg and summarized by visit using summary statistics for categorical variables. A cumulative distribution curve of categorical change from baseline to Day 120E will be presented for 24-hour average ambulatory sBP.

A shift table for categorical hypertension classification between baseline and maximum post-baseline values will be presented for visits 14E, 16E, and all data for 24-hour average ambulatory sBP. This summary will also be presented by baseline diabetic status. The hypertension classifications to be used are given in Table .
Hourly and half-hourly ambulatory sBP time matched changes from baseline (Section 6.2.4) to Day 120E will be calculated and listed with clock time and half-hourly elapsed time from ABPM recording start time.

Subjects may have started ABPM at different times at different visits and this calculation controls for diurnal variation by evaluating the 24 hours as a continuum with the justification of being at steady state. Time matches will be made using windowing, where the closest quality accepted reading (including all automatic and manually initiated readings) at the baseline visit within 30 minutes will be selected as the baseline reading; if 2 readings are equidistant in time, the earlier will be selected. The time matched changes from baseline will then be grouped into half-hourly clock time intervals, based on the clock time of the post-baseline measurement, by averaging multiple observations for a subject within a single interval. Half-hourly clock time intervals will initiate at exactly 7 a.m.

Half-hourly ambulatory sBP and time matched changes from baseline will be summarized using summary statistics for continuous variables in 2 ways, firstly by visit and half-hourly elapsed time from ABPM recording start time, and secondly by visit and half-hourly clock time intervals. Mean ± SD half-hourly ambulatory sBP and time matched changes from baseline will be graphically displayed by half-hourly elapsed time from ABPM recording start time overlaying visit and separately by half-hourly clock time intervals overlaying visit. For the summaries and plots by half-hourly elapsed time from ABPM recording start time, values based on manually initiated post-baseline readings will not be included. The window will be +/-0.25 nominal half hour increments and will be presented from zero to 23.5.

These tables and figures will be repeated including only subjects with non-missing results at all of Visits 7E, 14E and 16E (ABPM completers).

10.3.2. Daytime and Nighttime Average Ambulatory sBP

Daytime average ABPM values will be calculated from individual ABPM values between 7 a.m. and <11 p.m., nighttime average ABPM values will be calculated from individual ABPM values between 11 p.m. and <7 a.m. Secondary analyses will be on daytime and nighttime average ambulatory sBP after approximately 120 (±3) days of treatment in the MRS-TU-2019EXT study. The average values and changes from baseline will be summarized by visit using summary statistics for continuous variables, including 95% CIs for the means.

Box plots of daytime and nighttime average ambulatory sBP will be presented overlaying visit. Cumulative distribution curves of daytime and nighttime average ambulatory sBP will be presented overlaying visit.

Mixed model repeated measures analyses on the daytime and nighttime average ambulatory sBP will be performed with subject as a random effect (all subjects with non-missing post-baseline results), and visit (7E, 14E and 16E), MRS-TU-2019 prior randomized treatment (SOV2012-F1, AndroGel, or None for MRS-TU-2019 naïve subjects), and baseline hypertensive treatment status as fixed effects. Additional effects such as baseline diabetic status (Section 6.6) will be considered for inclusion. An unstructured covariance structure will be used to model the within-subject errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The least squares mean at each visit and the least squares mean for the difference between Day 120E and Day 1E with the associated 95% CIs will be provided for the daytime and nighttime average ambulatory sBP. Goodness of fit will be evaluated. A sensitivity analysis will be performed only including subjects with non-missing valid results at all of Visits 7E, 14E and 16E (ABPM completers).

These summaries and analyses on the 24-hour, daytime and nighttime average ambulatory sBP will also be presented for the subgroups detailed in Section 6.6, as data permit (minimum of 5 subjects per subgroup).

Separate Forest plots of daytime average, nighttime average, and 24-hour average ambulatory sBP will be provided, each presenting the least squares mean differences between visits with 95% CIs, including results from both the analysis on all subjects with non-missing post-baseline results and the analysis on ABPM completers.

Daytime average change from baseline ambulatory sBP values will be categorized into 5 mmHg increments to ±20 mmHg and summarized by visit using summary statistics for categorical variables. A cumulative distribution curve of categorical change from baseline to Day 120E will be presented for 24-hour average ambulatory sBP.

A shift table for categorical hypertension classification between baseline and maximum post-baseline values will be presented for daytime average ambulatory sBP. This summary will also be presented by baseline diabetic status. The hypertension classifications to be used are given in Table .

10.3.3. Censoring

All tables and figures will be repeated censoring for antihypertensive therapy changes, where profiles that were collected on or after the date of addition of or an increase in dosage of antihypertensive medications will be excluded after first dose of study drug in MRS-TU-2019EXT (Section 6.2.1). Antihypertensive medication restarted after any interruption at the same antihypertensive dose will not be counted as an addition. Censoring will not be done for summaries focusing on the washout time between studies.

10.3.4. Other Ambulatory sBP Endpoints

Other endpoints for ambulatory sBP are:

- Change from baseline in 24-hour average ambulatory sBP after approximately 180 (±3) days of treatment
- Change from baseline in daytime (Section 10.3.2) average ambulatory sBP after approximately 180 (±3) days of treatment.
- Change from baseline in nighttime (Section 10.3.2) average ambulatory sBP after approximately 180 (±3) days of treatment.
- Observed and change from baseline in half-hourly ambulatory sBP after approximately 180 (±3) days of treatment.

Ambulatory sBP at Day 180E will be evaluated in a similar fashion to the primary ABPM endpoint of sBP at Day 120E. Additionally, in the mixed model repeated measures analyses, the least squares mean for the difference between Day 180E and Day 120E will be provided with the associated 95% CI.

10.3.5. Effect of Dose on Average ABPM sBP

For Visit 14E (Day 120E) and Day 180E(Visit 16E), 24-hour average systolic and daytime average systolic will be broken down by the subject's dose. Observed and change from baseline will be summarized using summary statistics for continuous variables. Box plots of the changes from baseline for each of the visits will overlay the dose groups.

Further exploratory ANCOVA using the EXTS may be performed to evaluate the impact of baseline covariates including weight, baseline diabetic status, baseline hypertensive treatment status, age and dose on changes in 24 hour ABPM.

10.3.6. C_{avg} and Average ABPM sBP

Using the EXPK Set, scatter plots of the observed and change from baseline ABPM Day 120E 24 hour average systolic blood pressure versus Day 90E 24 hour C_{avg} will be produced. This will include an overlayed regression line with slope (95% CI) and adjusted R-square. This will also be done for the daytime average.

10.3.7. Estimation of Treatment Effects on ABPM sBP After a Year of Treatment

In order to estimate 24-hour, daytime, and nighttime average ambulatory sBP changes after a year of treatment, the values at Day 365 (after a year of treatment) and Day 6E/7E (after at least 8 weeks washout and simulating baseline) for continuing SOV2012-F1 subjects will be summarized using summary statistics for continuous variables, including 95% CIs for the means. The difference in least squares means between the 2 visits (Day 365-Day 6E/7E) and associated 95% CI will be determined through a mixed model analysis to simulate change from baseline values. Baseline hypertensive treatment status, and baseline diabetic status (Section 6.6) will be considered for inclusion as fixed effects. An unstructured covariance structure will be used to model the within-subject errors. The Kenward Roger approximation will be used to estimate denominator degrees of freedom. Analysis will not be repeated for any washout censoring.

10.3.8. Ambulatory dBP

Ambulatory dBP will be evaluated in a similar fashion to the ambulatory sBP.

10.3.9. Ambulatory Heart Rate (HR)

The 24-hour average ambulatory HR and changes from baseline will be summarized by visit using summary statistics for continuous variables, including 95% CIs for the means.

To evaluate central tendency and outliers, a box plot of 24-hour average ambulatory HR will be presented overlaying visit.

In addition, a mixed model repeated measures analysis on the 24-hour average ambulatory HR will be performed with subject as a random effect (all subjects with non-missing post-baseline results), and visit (7E, 14E and 16E), MRS-TU-2019 prior randomized treatment (SOV2012-F1, AndroGel, or None for MRS-TU-2019 naïve subjects), and baseline hypertensive treatment status. Additional effects such as baseline diabetic status (Section 6.6) will be considered for inclusion. An unstructured covariance structure will be used to model the within-subject errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The least squares mean at each visit and the least squares mean for the difference between Day 120E and Day 1E with the associated 95% CIs will be provided. Goodness of fit will be evaluated.

These summaries and analyses will also be presented for the subgroups detailed in Section 6.6, as data permit (minimum of 5 subjects per subgroup).

24-hour average change from baseline ambulatory HR values will be categorized into 5 bpm increments to ±20 bpm and summarized by visit using summary statistics for categorical variables.

Hourly and half-hourly ambulatory HR time matched changes from baseline (Section 6.2.4) to Day 120E and Day 180E will be calculated and listed with clock time and half-hourly elapsed time from ABPM recording start time. Time matches will be made using windowing, where the closest quality accepted reading (including all automatic and manually initiated readings) at the baseline visit within 30 minutes will be selected as the baseline reading; if 2 readings are equidistant in time, the earlier will be selected. The time matched changes from baseline will then be grouped into half-hourly clock time intervals, based on the clock time of the post-baseline measurement, by averaging multiple observations for a subject within a single interval. Half-hourly clock time intervals will initiate at exactly 7 a.m.

Half-hourly ambulatory HR and time matched changes from baseline will be summarized using summary statistics for continuous variables in 2 ways, firstly by visit and half-hourly elapsed time from ABPM recording start time, and secondly by visit and half-hourly clock time intervals. Mean ± SD half-hourly ambulatory HR and time matched changes from baseline will be graphically displayed by half-hourly elapsed time from ABPM recording start time overlaying visit and separately by half-hourly clock time intervals overlaying visit. For the summaries and plots by half-hourly elapsed time from ABPM recording start time, values based on manually initiated post-baseline readings will not be included. The window will be +/-0.25 nominal half hour increments and will be presented from zero to 23.5.

All tables and figures will be repeated censoring for antihypertensive therapy changes, where profiles that were collected on or after the date of addition of or an increase in dosage of antihypertensive medications will be excluded after first dose of study drug in MRS-TU-2019EXT (Section 6.2.1). Antihypertensive medication restarted after any interruption at the same antihypertensive dose will not be counted as an addition.

10.3.10. Ambulatory Mean Arterial Pressure (MAP)

Ambulatory MAP will be evaluated in a similar fashion to the ambulatory HR. In addition, a cumulative distribution curve of 24-hour average ambulatory MAP will be presented overlaying visit. A mixed model repeated measures sensitivity analysis will also be performed on ABPM completers.

A Forest plot of 24-hour average ambulatory MAP will be provided, presenting the least squares mean differences between visits with 95% CIs, including results from both the analysis on all subjects with non-missing post-baseline results and the analysis on ABPM completers.

10.3.11. Ambulatory Pulse Pressure (PP)

Ambulatory PP will be evaluated in a similar fashion to the ambulatory MAP.

10.4. T C_{MAX}

10.4.1. MRS-TU-2019

Analyses will be performed using the FAS.

Plasma T C_{max} after 90 days of treatment will be evaluated by estimating the percentage of SOV2012-F1-treated subjects at Visit 8, Day 90 with:

a) T $C_{max} \leq 1.5$xULN.

b) T $C_{max} > 1.8$x ULN and ≤ 2.5 xULN.

c) T $C_{max} > 2.5$ xULN .

Where ULN is the upper limit of normal as determined from the MRS-TNR2019 study.

The T C_{max} will be calculated per Section 9.4.1. Missing T C_{max} values at Day 90 (Visit 8) in the FAS will not be imputed.

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

Serum T C_{max} values for those subjects randomly assigned to receive AndroGel will also be summarized using the following ranges (units ng/dL)

a) T $C_{max} \leq 1500$.

b) T $C_{max} > 1800$ and ≤ 2500.

c) T $C_{max} > 2500$.

10.4.2. MRS-TU-2019EXT

Analyses will be performed using the mEXTS.

Plasma T C_{max} after 90 days of treatment will be evaluated by estimating the percentages of SOV2012-F1–treated subjects at Visit 12E, Day 90E with:

a) T $C_{max} \leq 1.5$x ULN.

b) T $C_{max} > 1.8$x ULN and ≤ 2.5x ULN.

c) T $C_{max} > 2.5$ xULN .

Where ULN is the upper limit of normal as determined from the MRS-TNR2019 study

The T C_{max} will be calculated per Section 9.4.1. Missing T C_{max} values at Day 90E (Visit 12E) in the EXTS will not be imputed.

Similar analyses will be performed for the EXTS, ESXE, mEXSE and EXPK.

Serum C_{max} values will use the following ranges:

a) T $C_{max} \leq 1500$.

b) T $C_{max} > 1800$ and ≤ 2500.

c) T $C_{max} > 2500$.

Subjects with Visit 12E Plasma T Cmax Over 1200 ng/dL will be listed separately.

10.5. ADVERSE EVENTS (AES)

AEs will be coded using MedDRA Version 20.0 or later.

TEAE definitions:

- An AE will be considered treatment-emergent if it begins or worsens in severity after the first dose of any study drug.
- An AE will be considered MRS-TU-2019 treatment-emergent if it begins or worsens in severity after the first dose of randomized study drug, and before the first dose of any study drug in MRS-TU-2019EXT.
- An AE will be considered MRS-TU-2019EXT treatment-emergent if it begins or worsens in severity after the first dose of study drug in MRS-TU-2019EXT.

- An AE will be considered SOV2012-F1 treatment-emergent if it begins or worsens in severity after the first dose of SOV2012-F1.

First dose dates of study drug are defined in Section 6.2.1. Partial AE start dates will be imputed as detailed in Section 6.3.5.

TEAEs will be summarized for both studies combined (SOV2012-F1 TEAEs only for all subjects in the OSS and for all subjects who took SOV2012-F1 in both studies), and separately for the MRS-TU-2019 study by MRS-TU-2019 treatment group and the MRS-TU-2019EXT study. TEAEs will be summarized by SOC and PT. Subjects will be counted once at the SOC level and once at each PT within the SOC level. Where applicable, summaries will include the number and percentage of subjects who report at least one TEAE, the number and percentage of subjects reporting at least one TEAE in a SOC, the number and percentage of subjects reporting at least one TEAE in a PT, and the total number of events within a SOC and within a PT. Tables will be sorted by decreasing frequency (overall) of SOC, and then, within a SOC, descending frequency (overall) of PT.

Overall summary tables of TEAEs will be presented detailing the number and percentage of subjects, and number of events for the following categories:

- At least one TEAE;
- Serious TEAEs;
- Treatment-related TEAEs;
- Treatment-related serious TEAEs;
- Severe TEAEs;
- Treatment-related severe TEAEs;
- TEAEs leading to discontinuation from study drug;
- TEAEs resulting in death;
- MACE;
- TEAEs of Hypertension or BP Increased;
- TEAEs of special interest (depression, anger, aggression and suicidality events**).**

The incidence of TEAEs by SOC and PT will be presented for the following:

- All TEAEs;
- Serious TEAEs;
- Treatment-related TEAEs;
- TEAEs leading to discontinuation from study drug;
- TEAEs of special interest (depression, anger, aggression and suicidality events**).**

Summaries of all TEAEs by maximum severity (mild, moderate, severe), SOC, and PT will be presented, where the maximum severity per subject will be counted at each level of summarization.

Relationships of 'possible' and 'probable' for AEs will be judged as being treatment-related for the summary tables. If the relationship to study drug is missing for TEAEs then the relationship will be counted as probably related to study drug for the summary tables. Similarly, missing severity for TEAEs will be counted as 'Severe'.

MACE are defined as non-fatal myocardial infarction, non-fatal cerebrovascular accident, and death due to cardiovascular disease. MACE will be summarized for both studies combined (MACE on SOV2012-F1 only for all subjects in the OSS and for all subjects who took SOV2012-F1 in both studies), and separately for the MRS-TU-2019 study by MRS-TU-2019 treatment group and the MRS-TU-2019EXT study. MACE summaries will be presented detailing the number and percentage of subjects, and number of events for the following categories:

- At least one MACE.
- Non-fatal myocardial infarction.
- Non-fatal cerebrovascular accident.
- Death due to cardiovascular disease.

Only TEAEs will be included in the AE summary tables, however all AEs will be included in the listings. In the listings, AE duration is calculated as date of adverse event stop – date of adverse event start + 1. MRS-TU-2019 TEAEs and MRS-TU-2019EXT TEAEs will be flagged in the listings. Additional listings will be provided for deaths, Serious TEAEs, TEAEs resulting in discontinuation from study drug, and TEAEs of hypertension or BP increased.

10.6. LABORATORY EVALUATIONS

Laboratory tests will be performed at Screening and periodically throughout the studies as described in the Flowcharts in Section 3.8. Laboratory tests within each category and scheduled visit are given in Table 11.

Table 11: Laboratory Tests and Scheduled Study Visits

Laboratory Category	Laboratory Tests Included	Scheduled Study Visit
Hematology	Hemoglobin, hematocrit, WBC and platelets	Screening Visit 2, Visit 8, Visit 10, Visit 12, EOT, Visit 7E, Visit 12E, Visit 16E, Early Withdrawal Visit E
Hematology	HbA1c	Screening Visit 2, EOT, Visit 7E, Visit 12E, Visit 16E
Biochemistry	AST, ALP, ALT, TB, creatinine, blood urea nitrogen, estimated glomerular filtration rate (eGFR), lactate dehydrogenase, glucose, total protein, albumin, sodium, potassium, calcium, and phosphorous	Screening Visit 2, Visit 4, Visit 6, Visit 8, Visit 10, Visit 12, EOT, Visit 7E, Visit 12E, Visit 16E, Early Withdrawal Visit E
Lipid Panel	Total cholesterol, low-density lipoproteins, high-density lipoproteins, and triglycerides	Screening Visit 2, Visit 4, Visit 6, Visit 8, Visit 10, Visit 12, EOT, Visit 7E, Visit 12E, Visit 16E
Endocrinology	LH, FSH, SHBG, and TSH	Screening Visit 2, Visit 8, EOT, Visit 7E, Visit 12E, Visit 16E, Early Withdrawal Visit E
Urinalysis	pH, glucose, ketones, blood, protein, microscopy, and specific gravity	Screening Visit 2
Other	Urine drug screen, screening for hepatitis B virus surface antigen, HCV antibody, and HIV antibody	Screening Visit 2
Serum PSA	PSA	Screening Visit 2, Visit 8, Visit 10, Visit 12,

EOT, Visit 7E, Visit 12E, Visit 16E, Early Withdrawal Visit E

Conventional units will be used for all listings and summaries, unless otherwise stated. Standard International units will also be included in the datasets.

All laboratory data will be listed, with abnormal results also listed separately. In addition, a listing will be presented for hemoglobin abnormal results and results of special concern, including and flagging hemoglobin results with increases from baseline (Section 6.2.4) of >0.5 g/dL.

10.6.1. MRS-TU-2019

Actual (observed) values and changes from baseline (Section 6.2.4) in continuous biochemistry, hematology, lipid panel, serum PSA, and endocrinology laboratory parameters will be summarized by treatment group at each scheduled visit. The number and percentage of subjects with laboratory measurements (except serum PSA) outside of the normal reference range will also be summarized by treatment group and visit. Shift tables from baseline to each scheduled visit will be used to evaluate changes in laboratory test values (except serum PSA) with respect to normal reference ranges (below, within, above the normal reference range).
Actual (observed) values and changes from baseline (Section 6.2.4) in HbA1c will be summarized by treatment group at each scheduled visit by baseline diabetic status (Section 6.6).

Subjects with serum PSA≥4.0 ng/mL or change from baseline in serum PSA>1.4 ng/mL will be listed and summarized using summary statistics for categorical variables, at any time and by visit.

Actual (observed) values in urinalysis and other laboratory parameters measured at screening only will be summarized by treatment group.

10.6.2. MRS-TU-2019EXT

Actual (observed) values and changes from MRS-TU-2019EXT baseline (Section 6.2.4) in continuous biochemistry, hematology, lipid panel, serum PSA, and endocrinology laboratory parameters will be summarized by MRS-TU-2019EXT visit. The number and percentage of subjects with laboratory measurements (except serum PSA) outside of the normal reference range will also be summarized by visit. Shift tables from baseline to each scheduled visit will be used to evaluate changes in laboratory test values (except serum PSA) with respect to normal reference ranges (below, within, above the normal reference range).

Actual (observed) values and changes from MRS-TU-2019EXT baseline (Section 6.2.4) in HbA1c will be summarized by MRS-TU-2019EXT visit and baseline diabetic status (Section 6.6).
Subjects with serum PSA≥4.0 ng/mL or change from baseline in serum PSA>1.4 ng/mL will be listed and summarized using summary statistics for categorical variables, at any time and by visit.

Actual (observed) values in urinalysis and other laboratory parameters measured at screening only will also be summarized.

10.7. LIVER TOXICITY

For MRS-TU-2019, the number and percentage of subjects in each treatment group with liver function tests (AST, ALT, and TB) greater than 1, 2, and 3 times the ULN at each study visit will be presented for the SS.

For MRS-TU-2019EXT, the number and percentage of subjects with liver function tests (AST, ALT, and TB) greater than 1, 2, and 3 times the ULN at each study visit will be presented for the EXTS.

Evaluation of drug-induced serious hepatotoxicity (eDISH) log-log plots of peak post-baseline TB (x ULN) vs. peak post-baseline AST (x ULN), and vs. peak post-baseline ALT (x ULN) will be presented for MRS-TU-2019 for the SS by treatment group, and eDISH log-log plots of peak post-baseline TB (x ULN) vs. peak post-baseline AST (x ULN), and vs. peak post-baseline ALT (x ULN) will be presented for MRS-TU-2019EXT for the EXTS. Reference lines will be displayed to show the normal range, and will be displayed at 2 times the ULN for peak post-baseline TB and 3 times the ULN for peak post-baseline AST or ALT to divide the plot into labelled quadrants. The cholestasis quadrant is where TB>2 x ULN and AST or ALT<3 x ULN, Temple's Corollary quadrant is where TB<2 x ULN and AST or ALT>3 x ULN, and Hy's Law quadrant is where TB>2 x ULN and AST or ALT>3 x ULN.

Liver function tests (AST, ALT, and TB) will be listed and values greater than 2 and 3 times the ULN will be flagged. In addition, subjects whose peak data lie in the cholestasis quadrant, Temple's Corollary quadrant, or Hy's Law quadrant for AST and/or ALT will be flagged.

10.8. VITAL SIGNS

10.8.1. MRS-TU-2019

Time 0 (Section 6.2.6) vital sign measurements including sBP, dBP, HR, and weight, and changes from baseline (Section 6.2.4), will be summarized at each scheduled visit by treatment group using summary statistics for continuous variables, including 95% CIs for the means. For sBP and dBP, where multiple

readings are taken at one timepoint, the mean of those readings will be used as the timepoint value in summaries and analyses. Means of 3 readings will be calculated in the database and truncated to whole numbers, means where there are only 2 readings will be calculated in SAS® and also truncated to whole numbers for consistency. These summaries will also be presented for the subgroups detailed in Section 6.6, where applicable, as detailed in Section 16.

Mean ± SD Time 0 sBP and dBP will be plotted at each scheduled fasting visit by treatment group, separately for observed and change from baseline values.

Mean ± SD change from baseline Time 0 sBP, dBP, and HR will be plotted for fasting visits, overlaying baseline hypertension classification (Table) by treatment group.

For sBP and dBP assessed at 4-hour intervals (Visits 4, 6 and 8 for subjects treated with SOV2012-F1 and Visit 8 for subjects treated with AndroGel, both at 0, 4, 8, 12, 16, 20 and 24 hours post-morning dose), 24-hour mean values and changes from baseline will be summarized by treatment group using summary statistics for continuous variables, including 95% CIs for the means, at each scheduled visit.

24-hour mean change from baseline sBP and dBP values will be categorized into 5 mmHg increments to ±20 mmHg and summarized by treatment group and visit using summary statistics for categorical variables. A cumulative distribution curve of categorical change from baseline to Day 90 overlaying treatment group will be presented for mean 24-hour sBP and for mean 24-hour dBP. Similar charts for categorical changes in mean 24-hour sBP and dBP for subjects treated with SOV2012-F1 will also be presented at Visits 4 and 6. The categories are presented in Table 12.

Table 12. Blood Pressure Categories

SBP Category Findings	DBP category findings	HR Category findings
<120	<80	<60
≥120-<130	≥80-<90	≥60-<80
≥130-<140	≥90	≥80-<100
≥140		≥100

Further exploratory analyses using MMRM methods may be performed to evaluate the impact of baseline covariates including, but not limited to, weight, baseline diabetic status, baseline hypertensive treatment status, age and dose including secondary interactive terms on changes in Time 0 sBP.

Hypertension

For sBP, dBP, and HR, shift tables for categorical hypertension classification between baseline (Section 6.2.4) and maximum post-baseline Time 0 values (using the mean value at timepoints where there are multiple readings) will be presented. In addition, the categorical hypertension classifications for each scheduled visit and the maximum post-baseline Time 0 values will be summarized by treatment group. These summaries will also be presented for the subgroups detailed in Section 6.6, where applicable, as detailed in Section 16.

The 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults[8] hypertension classifications to be used are given in Table 13 below.

Table 13:

Hypertensive Classifications
Normal: SBP <120 mmHg and DBP <80 mmHg
Elevated: SBP 120–129 mmHg and DBP <80 mmHg
Stage 1: Hypertension SBP 130–139 mmHg or DBP 80–89 mmHg (and SBP <140 and DBP <90 mmHg)
Stage 2 Hypertension SBP >=140 mmHg or DBP>=90 mmHg

Kaplan-Meier plots for the time in days from baseline to the first occurrence of a Stage 1 hypertensive event (date of first occurrence of Stage 1 hypertensive event-date of Visit 3) will be presented for each treatment group. This analysis will be limited to those subjects whose baseline hypertension status is normal or elevated. Subjects who do not experience Stage 1 hypertension during the study will be censored at the time of study withdrawal. Kaplan-Meier plots for the time in days from baseline to the first occurrence of a Stage 2 hypertensive event (date of first occurrence of Stage 2 hypertensive event-date of Visit 3) will also be presented for each treatment group. This analysis will be limited to those subjects whose baseline hypertension status is normal, elevated or Stage 1 hypertension.

Separate plots of mean values for sBP, dBP, and HR (left axis) will be overlaid with mean concentration values of T (right axis) versus time will be produced for Days 14, 42, and 90 for the SOV2012-F1 group and for Day 90 for the AndroGel group using the PKS.

These analyses may be repeated to include a confirmatory assessments at a separate visit following the elevation visit where the first assessment of an increase in hypertensive category was made in order to reflect clinical practice. The two visits must be at least within the range of the hypertensive elevation category unless the confirmatory visit is not available, in which case the hypertensive category will reflect the elevation visit assessment.

Censoring

All tables and figures will be repeated censoring for antihypertensive therapy changes, where measurements that were collected on or after the date of addition of or an increase in dosage of antihypertensive medications will be excluded after first dose of study drug (Section 6.2.1). Antihypertensive medication restarted after any interruption at the same antihypertensive dose will not be counted as an addition. For sBP and dBP assessed at 4-hour intervals, the whole profile will be censored if any of the measurements were collected on or after the date of addition of or an increase in dosage of antihypertensive medications after first dose of study drug (Section 6.2.1).

All vital signs data recorded will be listed. BMI at each visit after Screening Visit 2 will be calculated as weight (kg)/(height at Screening Visit 2 [m])^2 and also listed.

Effect of Dose on Time 0 sBP

For Day 90 and Day 180 , Time 0 systolic blood pressure will be broken down by the subject's dose. Observed and change from baseline will be summarized using summary statistics for continuous variables.

10.8.2. MRS-TU-2019EXT

Ambulatory BP, HR, MAP, and PP will be analyzed as detailed in Section 10.3.

Observed values collected in clinic (Time 0) vital sign measurements, including sBP, dBP, HR, and weight, and changes from baseline (Section 6.2.4), will be summarized by MRS-TU-2019EXT visit using summary statistics for continuous variables, including 95% CIs for the means. For sBP and dBP, where multiple readings are taken at one timepoint, the mean of those 3 readings will be calculated in the database, truncated to whole numbers, and used as the timepoint value in summaries and analyses. These summaries will also be presented for the subgroups detailed in Section 6.6, where applicable, as detailed in Section 16.

Mean ± SD sBP and dBP will be plotted at each scheduled visit, separately for observed and change from baseline values. To evaluate central tendency and outliers, box plots of sBP and dBP will be presented overlaying visit. Cumulative distribution curves of sBP and dBP will be presented overlaying visit.

Hypertension

For sBP, dBP, and HR, shift tables for categorical hypertension classification between baseline and maximum post-baseline Time 0 (Section 6.2.6) values (using the mean value at timepoints where there are multiple readings) will be presented. In addition, the categorical hypertension classifications for each scheduled visit and the maximum post-baseline Time 0 values will be summarized. These summaries will also be presented for the subgroups detailed in Section 6.6, where applicable, as detailed in Section 16.

The hypertension classifications to be used are given in Table 13.

Kaplan-Meier plots for the time in days from baseline to the first occurrence of a Stage 1 hypertensive event (date of first occurrence of Stage 1 hypertensive event-date of Visit 7E) will be presented. A Stage 1 hypertensive event will be defined if either Time 0 sBP or Time 0 dBP (using the mean values at timepoints where there are multiple readings) are classified as Stage 1 hypertension. This analysis will be limited to those subjects whose baseline hypertension status is normal or elevated. Subjects who do not experience Stage 1 hypertension during the study will be censored at the time of study early withdrawal. Kaplan-Meier plots for the time in days from baseline to the first occurrence of a Stage 2 hypertensive event (date of first occurrence of Stage 2 hypertensive event-date of Visit 7E) will also be presented. This analysis will be limited to those subjects whose baseline hypertension status is normal, elevated or Stage 1 hypertension.

These analyses may be repeated to include a confirmatory assessments at a separate visit following the elevation visit where the first assessment of an increase in hypertensive category was made in order to reflect clinical practice. The two visits must be at least within the range of the hypertensive elevation category unless the confirmatory visit is not available, in which case the hypertensive category will reflect the elevation visit assessment.

ABPM versus In Clinic

Scatter Plots of Time 0 in-clinic sBP and dBP versus 24-Hour average ambulatory sBP and dBP and versus daytime average ambulatory sBP and dBP at Visits 6E/7E, 13E/14E, and 15E/16E will be presented to assess the utility of in-clinic BP monitoring. Scatter Plots of Time 0 in-clinic change from baseline in sBP and dBP versus 24-Hour average change from baseline in ambulatory sBP and dBP and versus daytime average change from baseline in ambulatory sBP and dBP at 13E/14E, and 15E/16E will also be presented. A simple regression line will be displayed on each plot with the estimate of the slope and the p-value for the estimate of the slope.

ABPM versus Hemoglobin

Day 120E and Day 180E Scatter Plots of 24-Hour, Daytime and Nighttime average ambulatory sBP versus Day 90E hemoglobin will be presented. A simple regression line will be displayed on each plot with the estimate of the slope and the p value for the estimate of the slope. Similar analyses will be performed for the changes in sBP versus the changes in hemoglobin.

Washout

To determine the rate at which BP returns to steady state after discontinuation of TRT, sBP and dBP for continuing subjects will be summarized using summary statistics for continuous variables and presented as box plots by MRS-TU-2019 treatment group and overall for Visits 2E, 3E, 4E, 5E, and 6E.

Censoring

All tables and figures will be repeated censoring for antihypertensive therapy changes, where measurements that were collected on or after the date of addition of or an increase in dosage of antihypertensive medications will be excluded after first dose of study drug (Section 6.2.1). Antihypertensive medication restarted after any interruption at the same antihypertensive dose will not be counted as an addition.

All vital signs data recorded will be listed. BMI at each visit after Screening Visit 2 will be calculated as weight (kg)/(height at Screening Visit 2 [m])^2 and also listed.

Effect of Dose on Time 0 sBP

For Day 120E and Day 180E , Time 0 systolic blood pressure will be broken down by the subject's dose. Observed and change from baseline will be summarized using summary statistics for continuous variables.

10.9. ADRENOCORTICOTROPIC HORMONE (ACTH) SUB-STUDY

The ACTH analysis will be performed using the AAS.

The maximum serum cortisol (from the 30 minute and 60 minute post-cosyntropin measurements) will be calculated and summarized at Day 1 and at Week 52 by treatment group.

The maximum serum cortisol will be analyzed separately for each treatment group using a mixed effects model with visit as a fixed effect, baseline (Day 1 pre-cosyntropin) serum cortisol as a continuous covariate, and subject as a random effect. Differences in the least squares means of the comparisons between visits (Day 1 and Day 365) will be provided along with the 90% CIs.

The model assumptions of normality and homogeneity of variance will be investigated. If either assumption is clearly not satisfied, the model will be repeated using a log transformation, and ratios of Day 365 to Day 1 will be provided along with the 90% CIs.

10.10. OTHER SAFETY ASSESSMENTS

Physical examination data will be collected, as described in the Flowcharts in Section 3.8, and listed for all visits. Abnormal physical examination results will be listed separately. Abnormal physical examination results will be summarized using summary statistics for categorical variables by treatment group and visit for MRS-TU-2019 and by visit for MRS-TU-2019EXT.

12-Lead ECG data collected at Screening Visit 2, along with overall interpretation will be listed.

11. INTERIM ANALYSES

Interim analysis of the primary and secondary efficacy data, PK, and safety was planned for the 90-day efficacy period of the MRS-TU-2019 study to ensure all subjects were at the correct assigned dose. A high level of data cleaning was performed on the following data types: disposition, eligibility criteria, PDs, demography, PK, extent of exposure, meal records. The efficacy analyses and all outputs included in the interim analysis delivery were detailed in Version 2.0 of this SAP. For PK/efficacy/titration algorithm data, only data to Day 90 for available analytes were included and these data were considered final. For all other data, all data up to the data cut were included.

12. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

In the study protocol, MRS-TU-2019 is the original study described in the protocol body, and MRS-TU-2019EXT is described in an appendix to the protocol. Following discussion with the FDA, efficacy and safety analysis for labeling will be performed using the MRS-TU-2019EXT study, and therefore the parameters for effectiveness of SOV2012-F1 in the MRS-TU-2019 study have been removed, serum T C_{avg} and T C_{max} values for those subjects randomly assigned to receive AndroGel will be summarized only, and, in general within each section of TLFs, MRS-TU-2019EXT outputs are presented first, followed by MRS-TU-2019 outputs and then overall outputs.

Per FDA feedback, no multiple imputation methods will be used when there is not a post baseline 24 hour T C_{avg} As a result, the imputation for the primary endpoint in MRS-TU-2019EXT is a Worst Case Scenario since there are no 24 hour profiles in the extension study prior to Day 90E.

The population for the primary analysis of efficacy has been changed to a modified Extension Treated Set (mEXTS) to exclude site 104.

The modified Extension Serum Set (mEXSE) was added to exclude site 104.

The Extension PK Population was further clarified to exclude site 104.

For the calculation of the 24-hour T C_{avg}, the AUC_{0-24} will now be divided by 24, instead of the actual number of hours between dosing and the 24-hour sample collection time, because the AUC_{0-24} is calculated for AUC from Time 0 to exact time 24 hours with interpolation or extrapolation. If AUC_{0-24} is not calculable, and the T_{last} is close to 24 hours (between 23 and 25 hours inclusive), then $C_{avg0-last}$ will now be used for C_{avg}.

The secondary T C_{max} endpoint has been clarified to be a safety endpoint, rather than efficacy. Missing data will not be imputed and there will be no sensitivity analyses. The thresholds for SOV treated subjects will be set as (a) ≤1.5 x ULN; (b) 1.8 x ULN to 2.5 x ULN ; and (c) >2.5 x ULN after 90 days of treatment, where the ULN is defined using the NaF/EDTA plasma and serum endogenous testosterone from study MRS-TNR-2019. Androgel thresholds will remain as (a) <=1500, (b) 1800 to 2500, and (c) >2500 ng/dL.

The AUC_{0-24} ratios of DHT to T, and E2 to T, will not be calculated as these will be the same as the C_{avg} ratios of DHT to T, and E2 to T.

Sample size determination was updated to specify a non-inferiority test with a 3 mmHg upper boundary with respect to the 24-hour average in ambulatory sBP.

The MRS-TU-2019EXT secondary endpoints of maximum 24-hour sBP and dBP after approximately 120 days (±3) and 180 days (±3) of treatment were removed.

It has been clarified that ABPM analyses will be performed using 95% CIs.

Calculated ambulatory MAP and PP endpoints were added.

The SS was restricted to the MRS-TU-2019 study and the OSS was added for safety summaries across both studies with respect to SOV treated subjects. TEAEs will no longer be summarized separately for the washout period, instead, TEAE's during washout will be attributed to MRS-TU-2019.

The Extension Efficacy Completers Set was removed as it was too similar to the EXPK and no longer required. The sensitivity analysis of the primary MRS-TU-2019EXT efficacy endpoint will be performed using the EXPK Set.

inVentiv Health Clinic was changed to Syneos Health to reflect the change in company name.

Prior and concomitant medications will be coded using the WHO Drug B2 Format 01MAR2017 version, instead of the September 2012 WHO Drug Dictionary.

I-PSS, PDQ, SF-36, and IIEF summaries will be presented for the FAS instead of the SS as the interest lies in the change from baseline data.

The definition of the AAS was expanded to include only subjects who received correctly assigned study drug (including synthetic ACTH1-24 [cosyntropin]) and who had serum cortisol results at both Visit 3 and Day 365.

The ACTH Analysis Set was renamed to the ACTH Completer Analysis Set

Study drug compliance cannot be calculated as the actual number divided by the expected number of doses, as the actual number of doses will not be collected. Instead, overall study drug compliance (%) will be calculated separately for the MRS-TU-2019 study and the MRS-TU-2019EXT study and overall for SOV2012-F1 as 100*the overall actual dose consumed in the study divided by the overall expected dose for the study.

Mixed model repeated measures analyses on the 24-hour, daytime and nighttime average ambulatory vital signs will be performed instead of the more basic mixed model analyses suggested in the protocol.

The 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for defining hypertension replaced the previous definition. The analysis variable for the statistical analysis of the ACTH sub-study was changed, from the maximum increase from pre-cosyntropin administration, to the maximum serum cortisol. The change from baseline is not relevant, as a subject could have had a high baseline cortisol with little additional response to ACTH.

The interim analysis was originally planned for the Day 90 efficacy data, but then adjusted to also include all PK and selected safety data.

EXPK and PKS updated to require that subjects should be also be dosed.

13. REFERENCE LIST

1. SOV Therapeutics, Inc. Open-label, 4-part, Multiple-dose Study to Evaluate the Pharmacokinetic Profile, Safety, and Tolerability of Different Doses of Testosterone Undecanoate In Hypogonadal Subjects. Protocol SOV-TU-PK2013. On File. Morrisville, NC: SOV Therapeutics, Inc.; 25 November 2015.

2. End-of-Phase 2 Meeting. Pre-IND 118675; Testosterone Undecanoate (Oral) for the Treatment of Male Hypogonadism. SOV Therapeutics, Inc. 25 March 2015.

3. Vestergaard P, Hoeck HC, Jakobsen PE, Laurberg P. Reproducibility of Growth Hormone and Cortisol Responses to the Insulin Tolerance Test and the Short ACTH Test in Normal Adults. *Horm. Metab. Res.* 1997;29:106-110.

4. Oral testosterone undecanoate capsules (JATENZO™) for testosterone replacement therapy in hypogonadal men. Briefing document for Bone, Reproductive, and Urologic Drugs Advisory Committee. Advisory committee meeting date: 09 January 2018.

5. Quality Issue Summary Version 2.0. Marius Pharmaceuticals: 03Aug2018.

6. Vermeulen A, Verdonck L, Kaufman JM. A Critical Evaluation of Simple Methods for the Estimation of Free Testosterone in Serum. *J. Clin. Endocrinol. & Metab.* 1999;84(10):3666-3672.

7. Södergard R, et al., Calculation of Free and Bound Fractions of Testosterone and Estradiol-17ß to Human Plasma Proteins at Body Temperature. *J. steroid Biochem. 1982*;16:801-810.

8. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71:e13–e115. DOI: 10.1161/HYP.0000000000000065.

14. PROGRAMMING CONSIDERATIONS

All TLFs, and statistical analyses will be generated using SAS® for Windows, Release 9.4 (SAS® Institute Inc., Cary, NC, USA) or higher. Computer-generated TLF output will adhere to the following specifications.

PK parameters will be generated using WinNonLin Version 6.4 (Certara, USA).

14.1. GENERAL CONSIDERATIONS

- One SAS® program can create several outputs.
- Each output will be stored in a separate file, named using the following convention:
    - T14-X-X-YY for tables.
    - F14-X-X-YY for figures.
    - L16-X-X-YY for listings.

  Where X reflect the output numbering and YY is a mnemonic identifier for the type of output, e.g., DM for demography.
- Individual output files will be delivered in Rich Text File (RTF) format. Outputs will be collated in pdf format, separately for tables, listings, and figures.
- Numbering of TLFs will follow International Conference on Harmonization (ICH) E3 guidance
- Default SAS® output for all statistical analyses will be provided in RTF format from the same programs as the respective tables. Each output file will be named similarly to the corresponding table.

14.2. Table, Listing, and Figure (TLF) Format

14.2.1. General

- All TLFs will be produced in landscape format on American letter size pages, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch blank margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified

- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

14.2.2. Headers

- All output should have the following header at the top left of each page:

  <Sponsor Name> Protocol XXX
- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

14.2.3. Display Titles

Each TLF should be identified by the designation and a numeral, e.g., Table 14.1.1.1. ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination (see also template 03.007C “Table of Contents for Tables Listings and Figures in Statistical Analysis Plan”). A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(XXX Analysis Set)

14.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be SOV2012-F1 first, followed by AndroGel, then a total column (if applicable).

14.2.5. Body of the Data Display

General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

Table Conventions

Units will be included where available.

If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.

An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.

Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and SDs should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for sBP:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

P-values should be output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999

Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.

Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of AE data should be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by PT), drugs (by ATC1 code), and AEs (by PT) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated should be reported as "-".

The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

Where a category with a subheading (such as SOC) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.
- Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

14.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.

- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Subject specific footnotes should be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., ‘Program : myprogram.sas Listing source: 16.x.y.z’).

15. QUALITY CONTROL

SAS® programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health Standard Operating Procedure (SOP) Developing Statistical Programs (3907).

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS® programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS® programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

16. APPENDICES

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16.1.1. Index of Tables

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14.1.1.6	MRS-TU-2019EXT Subject Disposition	EXSE
14.1.1.7	MRS-TU-2019EXT Subject Disposition	mEXSE
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14.1.3.3.1.5	Medical History – Hypogonadism	mEXSE
14.1.3.3.1.6	Medical History – Hypogonadism	SS
14.1.3.3.1.7	Medical History – Hypogonadism	FAS
14.1.3.3.1.8	Medical History – Hypogonadism	PKS
14.1.3.3.1.9	Medical History – Hypogonadism	ECS
14.1.3.3.1.10	Medical History – Hypogonadism	AAS
14.1.3.3.1.11	Medical History – Hypogonadism	OSS
14.1.3.3.2.1	Medical/Surgical History	EXTS
14.1.3.3.2.2	Medical/Surgical History	EXPK
14.1.3.3.2.3	Medical/Surgical History	EXSE
14.1.3.3.2.4	Medical/Surgical History	SS
14.1.3.3.2.5	Medical/Surgical History	AAS
14.1.3.3.2.6	Medical/Surgical History	OSS
14.1.4.1.1	MRS-TU-2019EXT Prior Medications	EXTS
14.1.4.1.2	MRS-TU-2019EXT Prior Medications	mEXTS
14.1.4.1.3	MRS-TU-2019EXT Prior Medications	EXPK
14.1.4.1.4	MRS-TU-2019EXT Prior Medications	EXSE
14.1.4.1.5	MRS-TU-2019EXT Prior Medications	mEXSE
14.1.4.1.6	MRS-TU-2019 Prior Medications	SS
14.1.4.1.7	MRS-TU-2019 Prior Medications	FAS
14.1.4.1.8	MRS-TU-2019 Prior Medications	PKS
14.1.4.1.9	MRS-TU-2019 Prior Medications	ECS
14.1.4.1.10	MRS-TU-2019 Prior Medications	AAS
14.1.4.1.11	Overall Prior Medications	OSS
14.1.4.2.1	MRS-TU-2019EXT Concomitant Medications	EXTS
14.1.4.2.2	MRS-TU-2019EXT Concomitant Medications	mEXTS
14.1.4.2.3	MRS-TU-2019EXT Concomitant Medications	EXPK
14.1.4.2.4	MRS-TU-2019EXT Concomitant Medications	EXSE
14.1.4.2.5	MRS-TU-2019EXT Concomitant Medications	mEXSE
14.1.4.2.6	MRS-TU-2019EXT Concomitant Medications Taken up to the Day 90E Efficacy Visit	EXTS
14.1.4.2.7	MRS-TU-2019EXT Concomitant Medications Taken up to the Day 90E Efficacy Visit	mEXTS
14.1.4.2.8	MRS-TU-2019EXT Concomitant Medications Taken up to the Day 90E Efficacy Visit	EXPK

14.1.4.2.9	MRS-TU-2019EXT Concomitant Medications Taken up to the Day 90E Efficacy Visit	EXSE
14.1.4.2.10	MRS-TU-2019EXT Concomitant Medications Taken up to the Day 90E Efficacy Visit	mEXSE
14.1.4.2.11	MRS-TU-2019 Concomitant Medications	SS
14.1.4.2.12	MRS-TU-2019 Concomitant Medications	AAS
14.1.4.2.13	SOV2012-F1 Concomitant Medications	OSS
14.1.4.3.1	MRS-TU-2019EXT and MRS-TU-2019EXT Antihypertensive Medications	EXTS and SS
14.1.4.3.3	MRS-TU-2019EXT Treatment Emergent Antihypertensive Medications or Increases in Dose of Antihypertensive Medications	EXTS
14.1.4.3.4	MRS-TU-2019 Treatment Emergent Antihypertensive Medications or Increases in Dose of Antihypertensive Medications	SS
14.2.1.1.1	Primary MRS-TU-2019EXT Efficacy Parameter Plasma T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E) (Worst Case Scenario)	mEXTS
14.2.1.1.2	Primary MRS-TU-2019EXT Efficacy Parameter Plasma T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E): Primary Efficacy Analysis (Worst Case Scenario)	EXTS
14.2.1.1.3.1	Primary MRS-TU-2019EXT Efficacy Parameter Serum T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E) (Worst-Case Scenario)	EXSE
14.2.1.1.3.2	Primary MRS-TU-2019EXT Efficacy Parameter Plasma T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E) (Worst-Case Scenario)	EXSE
14.2.1.1.4.1	Primary MRS-TU-2019EXT Efficacy Parameter Serum T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E) (Worst-Case Scenario)	mEXSE
14.2.1.1.4.2	Primary MRS-TU-2019EXT Efficacy Parameter Plasma T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E) (Worst-Case Scenario)	mEXSE
14.2.1.1.5	Primary MRS-TU-2019EXT Efficacy Parameter Plasma T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E) (No Imputation)	EXPK

14.2.1.1.6.1	Primary MRS-TU-2019EXT Efficacy Parameter Plasma T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E): Subgroup Analysis Baseline by Weight Category(Worst Case Scenario)	EXTS
14.2.1.1.6.2	Primary MRS-TU-2019EXT Efficacy Parameter Plasma T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E): Subgroup Analysis by Age Category(Worst Case Scenario)	EXTS
14.2.1.1.6.3	Primary MRS-TU-2019EXT Efficacy Parameter Plasma T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E): Subgroup Analysis by BMI Category(Worst Case Scenario)	EXTS
14.2.1.1.6.4	Primary MRS-TU-2019EXT Efficacy Parameter Plasma T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E): Subgroup Analysis by Race Group(Worst Case Scenario)	EXTS
14.2.1.1.7.1	Primary MRS-TU-2019EXT Efficacy Parameter Plasma T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E): Subgroup Analysis by Weight Category(Worst Case Scenario)	mEXTS
14.2.1.1.7.2	Primary MRS-TU-2019EXT Efficacy Parameter Plasma T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E): Subgroup Analysis by Age Category(Worst Case Scenario)	mEXTS
14.2.1.1.7.3	Primary MRS-TU-2019EXT Efficacy Parameter Plasma T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E): Subgroup Analysis by BMI Category(Worst Case Scenario)	mEXTS
14.2.1.1.7.4	Primary MRS-TU-2019EXT Efficacy Parameter Plasma T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E): Subgroup Analysis by Race Group (Worst Case Scenario)	mEXTS
14.2.1.1.7.5	Primary MRS-TU-2019EXT Efficacy Parameter Plasma T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E): Subgroup Analysis by Actual Day 90E Breakfast Diet Category (Worst Case Scenario)	mEXTS
14.2.1.2	MRS-TU-2019EXT Pharmacokinetic Parameters	EXPK
14.2.1.2.1	MRS-TU-2019EXT Pharmacokinetic Parameters by Dose (Day 90)	EXPK
14.2.1.3.1	MRS-TU-2019 Summary of Observed and Change from Baseline in International Prostate Symptom Scores	FAS
14.2.1.3.2	MRS-TU-2019 Summary of Observed and Change from Baseline in Psychosexual Daily Questionnaire Scores	FAS
14.2.1.3.3	MRS-TU-2019 Summary of Observed and Change from Baseline in 36-Item Short Form Survey Instrument Scores	FAS

14.2.1.3.4	MRS-TU-2019 Summary of Observed and Change from Baseline in International Index of Erectile Function Questionnaire Scores	FAS
14.2.1.4	MRS-TU-2019 Fasting Insulin and Fasting Serum Glucose: Summary by Visit and Change from Baseline	SS
14.2.2.1.1.1.1	MRS-TU-2019EXT Pharmacokinetic Concentrations (ng/dL) by Visit and Timepoint – SOV2012-F1 Group	EXPK
14.2.2.1.1.1.2	MRS-TU-2019EXT Pharmacokinetic Concentrations (ng/dL) by Visit, Timepoint and Diet – SOV2012-F1 Group	EXPK
14.2.2.1.1.1.3	MRS-TU-2019EXT Pharmacokinetic Concentrations (ng/dL) by Visit, Timepoint and Dose– SOV2012-F1 Group	EXPK
14.2.2.1.1.2.1	MRS-TU-2019EXT Pharmacokinetic Plasma T, DHT, and E2 Concentrations (ng/dL) by Visit,Timepoint and Dose – SOV2012-F1	EXPK
14.2.2.1.2.2	MRS-TU-2019EXT Pharmacokinetic Parameters – Plasma T Cavg and T Cmax on Visit 12E (Day 90E) by Actual Day90E Breakfast Diet Category	EXPK
14.2.2.1.2.2.1	MRS-TU-2019EXT Pharmacokinetic Parameters – Plasma T $Cavg_{0-24}$ and T $Cmax_{0-24}$ on Visit 12E (Day 90E) Comparing Actual Day90E Breakfast Diet Categories	EXPK
14.2.2.1.2.2.2	MRS-TU-2019EXT Pharmacokinetic Parameters – Plasma T $Cavg_{0-12}$ and T $Cmax_{0-12}$ on Visit 12E (Day 90E) Comparing Actual Day90E Breakfast Diet Categories	EXPK
14.2.2.1.2.2.3	MRS-TU-2019EXT Pharmacokinetic Parameters - Listing of Plasma and Serum T Cavg0-24 and T Cmax0-24 on Visit 12E (Day 90E) for Low Fat Breakfast Diet Category Subjects	EXPK
14.2.2.1.2.3	MRS-TU-2019EXT Pharmacokinetic Parameters – Plasma T Cavg12-24 and T Cmax on Visit 12E (Day 90E) by Actual Day 90E Dinner Diet Category	EXPK
14.2.2.1.2.3.1	MRS-TU-2019EXT Pharmacokinetic Parameters – Plasma T $Cavg_{12-24}$ and T $Cmax_{12-24}$ on Visit 12E (Day 90E) Comparing Actual Day 90E Dinner Diet Categories	EXPK
14.2.2.1.2.4	MRS-TU-2019EXT Pharmacokinetic Parameters – Plasma T Cavg and T Cmax on Visit 12E (Day 90E) by Age Category	EXPK
14.2.2.1.2.6	MRS-TU-2019EXT Pharmacokinetic Parameters – Plasma T Cavg and T Cmax on Visit 12E (Day 90E) by Weight Category	EXPK
14.2.2.1.2.8	MRS-TU-2019EXT Pharmacokinetic Parameters – Plasma T Cavg and T Cmax on Visit 12E (Day 90E) by BMI Category	EXPK
14.2.2.1.2.10	MRS-TU-2019EXT Pharmacokinetic Parameters – Plasma T Cavg and T Cmax on Visit 12E (Day 90E) by Race	EXPK

14.2.2.1.2.12	MRS-TU-2019EXT Pharmacokinetic Parameters – Plasma T Cavg and T Cmax on Visit 12E (Day 90E) by Ethnicity	EXPK
14.2.2.1.2.14	MRS-TU-2019EXT Pharmacokinetic Parameters – Plasma DHT Cavg and DHT Cmax on Visit 12E (Day 90E)	EXPK
14.2.2.1.3.1	MRS-TU-2019EXT Analysis of Plasma T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E) by Visit 10E (Day 42E) Titration Timepoint	EXPK
14.2.2.1.3.2	MRS-TU-2019EXT Analysis of Projected Dose Adjustments Using Plasma T Concentrations by Visit and Timepoint	EXPK
14.2.2.1.3.2.1	MRS-TU-2019EXT Overall Plasma T Projected Dose Adjustment Analysis by 8E(Day 14E) and 10E(Day 42E) and Timepoint	EXPK
14.2.2.1.3.3	MRS-TU-2019EXT Analysis of Projected Dose Adjustments Using Serum T Concentrations by Visit and Timepoint	EXSE
14.2.2.1.3.3.1	MRS-TU-2019EXT Overall Serum T Projected Dose Adjustment Analysis by 8E(Day 14E) and 10E(Day 42E) and Timepoint	EXPK
14.2.2.1.3.4	MRS-TU-2019EXT Spearman's Correlation Matrix of Projected Dose Adjustments Using Plasma T Concentrations by Visit and Timepoint	EXPK
14.2.2.1.3.5	MRS-TU-2019EXT Spearman's Correlation Matrix of Projected Dose Adjustments Using Serum T Concentrations by Visit and Timepoint	EXPK-Serum
14.2.2.1.3.6	MRS-TU-2019EXT Logistic Analysis of Final Dose as an Outcome Variable	EXTS
14.2.2.1.3.7	MRS-TU-2019EXT Listing of Titration Outcomes with Respect to Serum and Plasma Concentrations	EXTS
14.2.2.1.3.7.1	MRS-TU-2019EXT Summary of Titration Outcomes with Respect to Serum and Plasma Concentrations	EXTS
14.2.2.1.4.1	MRS-TU-2019EXT Pharmacokinetic Parameters – Serum and Plasma T Cavg and T Cmax on Visit 12E (Day 90E)	EXPK-Serum
14.2.2.1.4.2	MRS-TU-2019EXT Pharmacokinetic Parameters – Serum and Plasma T Cavg and T Cmax on Visit 12E (Day 90E)	mEXSE
14.2.2.1.4.3	MRS-TU-2019EXT Analysis of Serum and Plasma T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E) by Visit 10E (Day 42E) Titration Timepoint	EXSE
14.2.2.1.4.4	MRS-TU-2019EXT Analysis of Serum and Plasma T Cavg Within the Normal Range After 90 Days of Treatment (Day 90E) by Visit 10E (Day 42E) Titration Timepoint	mEXSE
14.2.2.2.1.1	Primary MRS-TU-2019 Parameter T Cavg Within the Normal Range After 90 Days of Treatment (Day 90): Multiple Imputation Analysis	FAS

14.2.2.2.1.2	Primary MRS-TU-2019 Parameter T Cavg Within the Normal Range After 90 Days of Treatment (Day 90): (No Imputation)	ECS - SOV2012-F1-Treated Subjects
14.2.2.2.1.3	Primary MRS-TU-2019 Parameter T Cavg Within the Normal Range After 90 Days of Treatment (Day 90): (Worst-Case Scenario)	FAS - SOV2012-F1-Treated Subjects
14.2.2.2.2.1.1	MRS-TU-2019 Pharmacokinetic Plasma Concentrations (ng/dL) by Visit and Timepoint – SOV2012-F1 Group	PKS
14.2.2.2.2.2.1	MRS-TU-2019 Pharmacokinetic Plasma T, DHT, and E2 Concentrations (ng/dL) by Visit and Timepoint by Dose – SOV2012-F1 Group	PKS
14.2.2.2.2.2.2	MRS-TU-2019 Pharmacokinetic Plasma T Concentrations (ng/dL) by Visit and Timepoint by Breakfast Diet Categogry – SOV2012-F1 Group	PKS
14.2.2.2.2.2.3	MRS-TU-2019 Pharmacokinetic Plasma T Concentrations (ng/dL) by Visit and Timepoint by Dinner Diet Categogry – SOV2012-F1 Group	PKS
14.2.2.2.3.1	MRS-TU-2019 Pharmacokinetic Parameters – SOV2012-F1 Group	PKS
14.2.2.2.3.1.1	MRS-TU-2019 Pharmacokinetic Parameters by Dose– SOV2012-F1 Group (Day 90)	PKS
14.2.2.2.3.2	MRS-TU-2019 Pharmacokinetic Parameters – Plasma T Cavg and T Cmax on Visit 8 (Day 90) by Day 90 Breakfast Diet Category	PKS
14.2.2.2.3.2.1	MRS-TU-2019 Pharmacokinetic Parameters – Plasma T $Cavg_{0\text{-}24}$ and T $Cmax_{0\text{-}24}$ on Visit 8 (Day 90) Comparing Day 90 Breakfast Diet Categories	PKS
14.2.2.2.3.2.2	MRS-TU-2019 Pharmacokinetic Parameters – Plasma T $Cavg_{0\text{-}12}$ and T $Cmax_{0\text{-}12}$ on Visit 8 (Day 90) Comparing Day 90 Breakfast Diet Categories	PKS
14.2.2.2.3.2.3	MRS-TU-2019 Pharmacokinetic Parameters - Listing of Plasma T Cavg0-24 and T Cmax0-24 on Visit 8 (Day 90) for Low Fat Breakfast Diet Category Subjects	PKS
14.2.2.2.3.3	MRS-TU-2019EXT Pharmacokinetic Parameters – Plasma T Cavg12-24 and T Cmax on Visit 8 (Day 90) by Day 90 Dinner Diet Category	PKS
14.2.2.2.3.3.1	MRS-TU-2019EXT Pharmacokinetic Parameters – Plasma T $Cavg_{12\text{-}24}$ and T $Cmax_{12\text{-}24}$ on Visit 8 (Day 90) Comparing Day 90 Dinner Diet Category	PKS
14.2.2.3.1.1	MRS-TU-2019 Pharmacokinetic Concentrations (ng/dL) at Visit 8 (Day 90) by Timepoint – AndroGel Group	PKS
14.2.2.3.2.1	MRS-TU-2019 Pharmacokinetic Serum T, Serum DHT, and Plasma E2 Concentrations (ng/dL) at Visit 8 (Day 90) by Timepoint by Dose – Androgel Group	PKS

14.2.2.3.3	MRS-TU-2019 Pharmacokinetic Parameters – AndroGel Group	PKS
14.3.1.1.1	MRS-TU-2019EXT Treatment-Emergent Adverse Events –Overall Summary	EXTS
14.3.1.1.2	MRS-TU-2019EXT Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	EXTS
14.3.1.1.3	MRS-TU-2019EXT Treatment-Emergent Adverse Events by Frequency of Preferred Term	EXTS
14.3.1.1.4	MRS-TU-2019EXT Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	EXTS
14.3.1.1.5	MRS-TU-2019EXT Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	EXTS
14.3.1.1.6	MRS-TU-2019EXT Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	EXTS
14.3.1.1.7	MRS-TU-2019EXT Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study Drug by System Organ Class and Preferred Term	EXTS
14.3.1.1.8	Summary of MRS-TU-2019EXT Major Adverse Cardiac Events	EXTS
14.3.1.1.9	MRS-TU-2019EXT Treatment-Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term	EXTS
14.3.1.2.1	MRS-TU-2019 Treatment-Emergent Adverse Events – Overall Summary	SS
14.3.1.2.2	MRS-TU-2019 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	SS
14.3.1.2.3	MRS-TU-2019 Treatment-Emergent Adverse Events by Frequency of Preferred Term	SS
14.3.1.2.4	MRS-TU-2019 Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	SS
14.3.1.2.5	MRS-TU-2019 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	SS
14.3.1.2.6	MRS-TU-2019 Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	SS
14.3.1.2.7	MRS-TU-2019 Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study Drug by System Organ Class and Preferred Term	SS
14.3.1.2.8	MRS-TU-2019 Treatment-Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term	SS

14.3.1.2.9	Summary of MRS-TU-2019 Major Adverse Cardiac Events	SS
14.3.1.3.1	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Events – Overall Summary	OSS
14.3.1.3.1.1	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Events – Overall Summary by Baseline Age Category	OSS
14.3.1.3.1.2	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Events – Overall Summary by Baseline Weight Category	OSS
14.3.1.3.1.3	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Events – Overall Summary by Race	OSS
14.3.1.3.1.4	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Events – Overall Summary by Baseline Diabetic Status	OSS
14.3.1.3.1.5	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Events – Overall Summary by Baseline Hypertensive Treatment Status	OSS
14.3.1.3.2	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	OSS
14.3.1.3.2.1	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term and Baseline Age Category	OSS
14.3.1.3.2.2	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term and Baseline Weight Category	OSS
14.3.1.3.2.3	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term and Race	OSS
14.3.1.3.2.4	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term and Baseline Diabetic Status	OSS
14.3.1.3.2.5	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term and Baseline Hypertensive Treatment Status	OSS

14.3.1.3.3	MRS-TU-2019 and MRS-TU-2019EXT Treatment-Emergent Adverse Events by Frequency of Preferred Term	OSS
14.3.1.3.3.1	MRS-TU-2019 and MRS-TU-2019EXT Treatment-Emergent Adverse Events by Frequency of Preferred Term and Baseline Age Category	OSS
14.3.1.3.3.2	MRS-TU-2019 and MRS-TU-2019EXT Treatment-Emergent Adverse Events by Frequency of Preferred Term and Baseline Weight Category	OSS
14.3.1.3.3.3	MRS-TU-2019 and MRS-TU-2019EXT Treatment-Emergent Adverse Events by Frequency of Preferred Term and Race	OSS
14.3.1.3.3.4	MRS-TU-2019 and MRS-TU-2019EXT Treatment-Emergent Adverse Events by Frequency of Preferred Term and Baseline Diabetic Status	OSS
14.3.1.3.3.5	MRS-TU-2019 and MRS-TU-2019EXT Treatment-Emergent Adverse Events by Frequency of Preferred Term and Baseline Hypertensive Treatment Status	OSS
14.3.1.3.4	MRS-TU-2019 and MRS-TU-2019EXT Serious SOV2012-F1 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	OSS
14.3.1.3.5	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	OSS
14.3.1.3.5.1	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, Maximum Severity and Baseline Age Cateogry	OSS
14.3.1.3.5.2	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, Maximum Severity and Baseline Weight Category	OSS
14.3.1.3.5.3	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, Maximum Severity and Race	OSS
14.3.1.3.5.4	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, Maximum Severity and Baseline Diabaetic Status	OSS

14.3.1.3.5.5	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, Maximum Severity and Baseline Hypertensive Treatment Status	OSS
14.3.1.3.6	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	OSS
14.3.1.3.6.1	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline Age Category	OSS
14.3.1.3.6.2	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline Weight Category	OSS
14.3.1.3.6.3	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race	OSS
14.3.1.3.6.4	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline Diabetic Status	OSS
14.3.1.3.6.5	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline Hypertensive Treatment Status	OSS
14.3.1.3.7	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study Drug by System Organ Class and Preferred Term	OSS
14.3.1.3.8	MRS-TU-2019 and MRS-TU-2019EXT SOV2012-F1 Treatment-Emergent Adverse Eventsof Special Interest by System Organ Class and Preferred Term	OSS
14.3.1.3.9	Summary of MRS-TU-2019 and MRS-TU-2019EXT Major Adverse Cardiac Events on SOV2012-F1	OSS
14.3.2.1	Deaths, Listing	SS and EXTS
14.3.2.2	Serious Treatment-Emergent Adverse Events, Listing	SS and EXTS

14.3.2.3	Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study Drug, Listing	SS and EXTS
14.3.2.4	Treatment-Emergent Adverse Events of Hypertension or Blood Pressure Increased, Listing	SS and EXTS
14.3.3	Narratives of Deaths, Other Serious, and Certain Other Significant Adverse Events	N/A
14.3.4.1.1.1.1.1	MRS-TU-2019EXT Hematology: Summary by Visit and Change from Baseline	EXTS
14.3.4.1.1.1.1.2	MRS-TU-2019EXT Hematology: Summary by Visit and %Change from Baseline	EXTS
14.3.4.1.1.1.2	MRS-TU-2019EXT Hematology: Laboratory Parameters Outside Normal Reference Range by Study Visit	EXTS
14.3.4.1.1.1.3	MRS-TU-2019EXT Hematology: Shift from Baseline Relative to the Normal Reference Range	EXTS
14.3.4.1.1.1.4	MRS-TU-2019EXT Hematology: HbA1c (%) by Visit and Baseline Diabetic Status	EXTS
14.3.4.1.1.1.5	HbA1c (%) at Screening	EXTS
14.3.4.1.1.2.1.1	MRS-TU-2019 Hematology: Summary by Visit and Change from Baseline	SS
14.3.4.1.1.2.1.2	MRS-TU-2019 Hematology: Summary by Visit and Percent Change from Baseline	SS
14.3.4.1.1.2.2	MRS-TU-2019 Hematology: Laboratory Parameters Outside Normal Reference Range by Study Visit	SS
14.3.4.1.1.2.3	MRS-TU-2019 Hematology: Shift from Baseline Relative to the Normal Reference Range	SS
14.3.4.1.1.2.4	MRS-TU-2019 Hematology: HbA1c (%) by Visit and Baseline Diabetic Status	SS
14.3.4.1.1.2.5	HbA1c (%) at Screening	SS
14.3.4.1.1.3.1	Hematology: Abnormal Laboratory Results, Listing	SS and EXTS
14.3.4.1.1.3.2	Hemoglobin: Abnormal Results and Results of Special Concern, Listing	SS and EXTS
14.3.4.1.2.1.1.1	MRS-TU-2019EXT Biochemistry: Summary by Visit and Change from Baseline	EXTS
14.3.4.1.2.1.1.2	MRS-TU-2019EXT Biochemistry: Summary by Visit and % Change from Baseline	EXTS

14.3.4.1.2.1.2	MRS-TU-2019EXT Biochemistry: Laboratory Parameters Outside Normal Reference Range by Study Visit	EXTS
14.3.4.1.2.1.3	MRS-TU-2019EXT Biochemistry: Shift from Baseline Relative to the Normal Reference Range	EXTS
14.3.4.1.2.1.4	MRS-TU-2019EXT Biochemistry: Liver Function Tests Above Normal Reference Range by Study Visit	EXTS
14.3.4.1.2.2.1.1	MRS-TU-2019 Biochemistry: Summary by Visit and Change from Baseline	SS
14.3.4.1.2.2.1.2	MRS-TU-2019 Biochemistry: Summary by Visit and Percent Change from Baseline	SS
14.3.4.1.2.2.2	MRS-TU-2019 Biochemistry: Laboratory Parameters Outside Normal Reference Range by Study Visit	SS
14.3.4.1.2.2.3	MRS-TU-2019 Biochemistry: Shift from Baseline Relative to the Normal Reference Range	SS
14.3.4.1.2.2.4	MRS-TU-2019 Biochemistry: Liver Function Tests Above Normal Reference Range by Study Visit	SS
14.3.4.1.2.3.1	Biochemistry: Abnormal Laboratory Results, Listing	SS and EXTS
14.3.4.1.2.3.2	Biochemistry: Potential Liver Toxicity Events, Listing	SS and EXTS
14.3.4.1.3.1	MRS-TU-2019EXT Urinalysis: Screening Summary	EXTS
14.3.4.1.3.2	MRS-TU-2019 Urinalysis: Screening Summary	SS
14.3.4.1.3.3	Urinalysis: Abnormal Laboratory Results, Listing	SS and EXTS
14.3.4.1.4.1.1.1	MRS-TU-2019EXT Endocrinology: Summary by Visit and Change from Baseline	EXTS
14.3.4.1.4.1.1.2	MRS-TU-2019EXT Endocrinology: Summary by Visit and % Change from Baseline	EXTS
14.3.4.1.4.1.2	MRS-TU-2019EXT Endocrinology: Laboratory Parameters Outside Normal Reference Range by Study Visit	EXTS
14.3.4.1.4.1.3	MRS-TU-2019EXT Endocrinology: Shift from Baseline Relative to the Normal Reference Range	EXTS
14.3.4.1.4.2.1.1	MRS-TU-2019 Endocrinology: Summary by Visit and Change from Baseline	SS
14.3.4.1.4.2.1.2	MRS-TU-2019 Endocrinology: Summary by Visit and Percent Change from Baseline	SS
14.3.4.1.4.2.2	MRS-TU-2019 Endocrinology: Laboratory Parameters Outside Normal Reference Range by Study Visit	SS

14.3.4.1.4.2.3	MRS-TU-2019 Endocrinology: Shift from Baseline Relative to the Normal Reference Range	SS
14.3.4.1.4.3	Endocrinology: Abnormal Laboratory Results, Listing	SS and EXTS
14.3.4.1.5.1.1.1	MRS-TU-2019EXT Lipid Panel: Summary by Visit and Change from Baseline	EXTS
14.3.4.1.5.1.1.2	MRS-TU-2019EXT Lipid Panel: Summary by Visit and % Change from Baseline	EXTS
14.3.4.1.5.1.2	MRS-TU-2019EXT Lipid Panel: Laboratory Parameters Outside Normal Reference Range by Study Visit	EXTS
14.3.4.1.5.1.3	MRS-TU-2019EXT Lipid Panel: Shift from Baseline Relative to the Normal Reference Range	EXTS
14.3.4.1.5.2.1.1	MRS-TU-2019 Lipid Panel: Summary by Visit and Change from Baseline	SS
14.3.4.1.5.2.1.2	MRS-TU-2019 Lipid Panel: Summary by Visit and Percent Change from Baseline	SS
14.3.4.1.5.2.2	MRS-TU-2019 Lipid Panel: Laboratory Parameters Outside Normal Reference Range by Study Visit	SS
14.3.4.1.5.2.3	MRS-TU-2019 Lipid Panel: Shift from Baseline Relative to the Normal Reference Range	SS
14.3.4.1.5.3	Lipid Panel: Abnormal Laboratory Results, Listing	SS and EXTS
14.3.4.1.6.1.1.1	MRS-TU-2019EXT Serum PSA: Summary by Visit and Change from Baseline	EXTS
14.3.4.1.6.1.1.2	MRS-TU-2019EXT Serum PSA: Summary by Visit and % Change from Baseline	EXTS
14.3.4.1.6.1.2	MRS-TU-2019EXT Serum PSA: Summary of Percentage of Subjects with Serum PSA>=4 ng/mL and Percentage of Subjects with Change from Baseline in Serum PSA>1.4 ng/mL Anytime and by Visit	EXTS
14.3.4.1.6.2.1.1	MRS-TU-2019 Serum PSA: Summary by Visit and Change from Baseline	SS
14.3.4.1.6.2.1.2	MRS-TU-2019 Serum PSA: Summary by Visit and Percent Change from Baseline	SS
14.3.4.1.6.2.2	MRS-TU-2019 Serum PSA: Summary of Percentage of Subjects with Serum PSA>=4 ng/mL and Percentage of Subjects with Change from Baseline in Serum PSA>1.4 ng/mL Anytime and by Visit	SS
14.3.4.1.6.3	Serum PSA: Subjects with Serum PSA>=4 ng/mL or with Change from Baseline in Serum PSA>1.4 ng/mL, Listing	SS and EXTS

14.3.4.1.7.1.1	Urine Drug Screen	EXTS
14.3.4.1.7.1.2	Urine Drug Screen	SS
14.3.4.1.7.2.1	Hepatitis/HIV Screening	EXTS
14.3.4.1.7.2.2	Hepatitis/HIV Screening	SS
14.3.4.2.1.1.1.1	MRS-TU-2019EXT Summary of Time 0 Vital Signs and Change from Baseline by Visit (All Data and Censored)	EXTS
14.3.4.2.1.1.2.1	MRS-TU-2019EXT Summary of Time 0 Vital Signs and Change from Baseline by Visit and Baseline Diabetic Status (All Data and Censored)	EXTS
14.3.4.2.1.1.2.2	MRS-TU-2019EXT Summary of Time 0 Vital Signs and Change from Baseline by Visit and Baseline Hypertensive Status (All Data and Censored)	EXTS
14.3.4.2.1.1.2.3	MRS-TU-2019EXT Summary of Time 0 Vital Signs and Change from Baseline by Visit and Baseline Hypertensive Treatment Status (All Data and Censored)	EXTS
14.3.4.2.1.1.2.4	MRS-TU-2019EXT Summary of Time 0 Vital Signs and Change from Baseline by Visit and Baseline Hypogonadal Status (All Data and Censored)	EXTS
14.3.4.2.1.1.2.5	MRS-TU-2019EXT Summary of Time 0 Vital Signs and Change from Baseline by Visit and Baseline Statin Treatment Status (All Data and Censored)	EXTS
14.3.4.2.1.1.2.6	MRS-TU-2019EXT Summary of Time 0 Vital Signs and Change from Baseline by Visit and Age Group (All Data and Censored)	EXTS
14.3.4.2.1.1.2.7	MRS-TU-2019EXT Summary of Time 0 Vital Signs and Change from Baseline by Visit and Dose (All Data and Censored)	EXTS
14.3.4.2.1.2.1	MRS-TU-2019EXT Categorical Summary of Time 0 Vital Signs by Visit (All Data and Censored)	EXTS
14.3.4.2.1.2.2.1	MRS-TU-2019EXT Categorical Summary of Time 0 Vital Signs by Visit and Baseline Diabetic Status (All Data and Censored)	EXTS
14.3.4.2.1.2.2.2	MRS-TU-2019EXT Categorical Summary of Time 0 Vital Signs by Visit and Baseline Hypertensive Status (All Data and Censored)	EXTS
14.3.4.2.1.2.2.3	MRS-TU-2019EXT Categorical Summary of Time 0 Vital Signs by Visit and Baseline Hypertensive Treatment Status (All Data and Censored)	EXTS

14.3.4.2.1.2.2.4	MRS-TU-2019EXT Categorical Summary of Time 0 Vital Signs by Visit and Baseline Hypogonadal Status (All Data and Censored)	EXTS
14.3.4.2.1.2.2.6	MRS-TU-2019EXT Categorical Summary of Time 0 Vital Signs by Visit and Baseline Statin Treatment Status (All Data and Censored)	EXTS
14.3.4.2.1.2.2.7	MRS-TU-2019EXT Categorical Summary of Time 0 Vital Signs by Visit and Age Group (All Data and Censored)	EXTS
14.3.4.2.1.3.1	MRS-TU-2019EXT Time 0 Vital Signs: Shifts in Hypertension Classification between Baseline and Post-baseline Value (All Data and Censored)	EXTS
14.3.4.2.1.3.1.1	MRS-TU-2019EXT Time 0 Vital Signs: Shifts in Hypertension Classification between Baseline and Post-baseline Value Using Confirmatory Results (All Data and Censored)	EXTS
14.3.4.2.1.3.2.1	MRS-TU-2019EXT Time 0 Vital Signs: Shifts in Hypertension Classification between Baseline and Post-baseline Value by Baseline Diabetic Status (All Data and Censored)	EXTS
14.3.4.2.1.3.2.2	MRS-TU-2019EXT Time 0 Vital Signs: Shifts in Hypertension Classification between Baseline and Post-baseline Value by Baseline Hypertensive Status (All Data and Censored)	EXTS
14.3.4.2.1.3.2.3	MRS-TU-2019EXT Time 0 Vital Signs: Shifts in Hypertension Classification between Baseline and Post-baseline Value by Baseline Hypertensive Treatment Status (All Data and Censored)	EXTS
14.3.4.2.1.3.2.4	MRS-TU-2019EXT Time 0 Vital Signs: Shifts in Hypertension Classification between Baseline and Post-baseline Value by Baseline Hypogonadal Status (All Data and Censored)	EXTS
14.3.4.2.1.3.2.6	MRS-TU-2019EXT Time 0 Vital Signs: Shifts in Hypertension Classification between Baseline and Maximum Post-baseline Value by Baseline Statin Treatment Status (All Data and Censored)	EXTS
14.3.4.2.1.3.2.7	MRS-TU-2019EXT Time 0 Vital Signs: Shifts in Hypertension Classification between Baseline and Maximum Post-baseline Value by Age Group (All Data and Censored)	EXTS
14.3.4.2.1.4.3	MRS-TU-2019EXT Concordance Analysis of Hypertension of In Clinic Time 0 Blood Pressure versus 24 Hour Average ABPM	EXTS
14.3.4.2.1.4.4	MRS-TU-2019EXT Concordance Analysis of Hypertension of In Clinic Time 0 Blood Pressure versus Daytime Average ABPM	EXTS

14.3.4.2.1.7.1	MRS-TU-2019EXT Summary of Time 0 Blood Pressure by MRS-TU-2019 Treatment Group and Washout Visit (All Data)	All Continuing Subjects
14.3.4.2.2.1.1	MRS-TU-2019 Summary of Time 0 Vital Signs and Change from Baseline by Visit (All Data and Censored)	SS
14.3.4.2.2.1.2.1	MRS-TU-2019 Summary of Time 0 Vital Signs and Change from Baseline by Visit and Baseline Hypertensive Status (All Data and Censored)	SS
14.3.4.2.2.1.2.2	MRS-TU-2019 Summary of Time 0 Vital Signs and Change from Baseline by Visit and Baseline Hypertensive Treatment Status (All Data and Censored)	SS
14.3.4.2.2.1.2.3	MRS-TU-2019 Summary of Time 0 Vital Signs and Change from Baseline by Visit and Dose (All Data and Censored)	SS
14.3.4.2.2.3	MRS-TU-2019 Summary of 24-hour Mean Blood Pressure and Change from Baseline by Visit (All Data and Censored)	SS
14.3.4.2.2.3.1	MRS-TU-2019 Summary of Day 90 24-hour Mean Blood Pressure and Change from Baseline by Day 90 Hgb Tertiles (All Data)	SS
14.3.4.2.2.4.1	MRS-TU-2019 Categorical Summary of Change from Baseline in 24-hour Mean Blood Pressure by Visit (All Data and Censored)	SS
14.3.4.2.2.5.1	MRS-TU-2019 Categorical Summary of Time 0 Vital Signs by Visit (All Data and Censored)	SS
14.3.4.2.2.5.2	MRS-TU-2019 Categorical Summary of Time 0 Vital Signs by Visit and Baseline Hypertensive Treatment Status (All Data and Censored)	SS
14.3.4.2.2.5.3	MRS-TU-2019 Time 0 Vital Signs: Shifts in Hypertension Classification between Baseline and Post-baseline Value (All Data and Censored)	SS
14.3.4.2.2.5.3.1	MRS-TU-2019 Time 0 Vital Signs: Shifts in Hypertension Classification between Baseline and Post-baseline Value with Confirmatory Results (All Data and Censored)	SS
14.3.4.3.1.1.1.1.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of 24-hour Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline by Visit (All Data and Censored)	EXTS
14.3.4.3.1.1.1.1.2	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mixed Model Repeated Measures Analysis of 24-hour Average Ambulatory Systolic Blood Pressure (mmHg) (All Data and Censored)	EXTS

14.3.4.3.1.1.1.1.3	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mixed Model Repeated Measures Analysis of 24-hour Average Ambulatory Systolic Blood Pressure (mmHg) (All Data and Censored): Sensitivity Analysis (ABPM Completers)	EXTS - ABPM Completers
14.3.4.3.1.1.1.2.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of Daytime and Nighttime Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline by Visit (All Data and Censored)	EXTS
14.3.4.3.1.1.1.2.2	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mixed Model Repeated Measures Analysis of Daytime Average Ambulatory Systolic Blood Pressure (mmHg) (All Data and Censored)	EXTS
14.3.4.3.1.1.1.2.3	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mixed Model Repeated Measures Analysis of Daytime Average Ambulatory Systolic Blood Pressure (mmHg) (All Data and Censored): Sensitivity Analysis (ABPM Completers)	EXTS - ABPM Completers
14.3.4.3.1.1.1.2.4	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mixed Model Repeated Measures Analysis of Nighttime Average Ambulatory Systolic Blood Pressure (mmHg) (All Data and Censored)	EXTS
14.3.4.3.1.1.1.2.5	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mixed Model Repeated Measures Analysis of Nighttime Average Ambulatory Systolic Blood Pressure (mmHg) (All Data and Censored): Sensitivity Analysis (ABPM Completers)	EXTS - ABPM Completers
14.3.4.3.1.2.1.1	MRS-TU-2019EXT Categorical Summary of 24-hour Average Ambulatory Systolic Blood Pressure by Visit (All Data and Censored) (Extension Treated Set)	EXTS
14.3.4.3.1.2.1.2	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Categorical Summary of Change from Baseline in 24-hour Average Ambulatory Systolic Blood Pressure (mmHg) by Visit (All Data and Censored)	EXTS
14.3.4.3.1.2.2.1	MRS-TU-2019EXT Categorical Summary of Daytime Average Ambulatory Systolic Blood Pressure by Visit (All Data and Censored) (Extension Treated Set)	EXTS

14.3.4.3.1.2.2.2	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Categorical Summary of Change from Baseline in Daytime Average Ambulatory Systolic Blood Pressure (mmHg) by Visit (All Data and Censored)	EXTS
14.3.4.3.1.3.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Blood Pressure: Shifts in Hypertension Classification between Baseline and Maximum Post-baseline Value in 24-Hour Average Ambulatory Blood Pressure (All Data and Censored) (All Data and Censored)	EXTS
14.3.4.3.1.3.2	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Blood Pressure: Shifts in Hypertension Classification between Baseline and Maximum Post-baseline Value in 24-Hour Average Ambulatory Blood Pressure (All Data and Censored) by Baseline Diabetic Status (All Data and Censored)	EXTS
14.3.4.3.1.3.3	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Blood Pressure: Shifts in Hypertension Classification between Baseline and Maximum Post-baseline Value in Daytime Average Ambulatory Systolic Blood Pressure (mmHg) (All Data and Censored)	EXTS
14.3.4.3.1.3.4	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Blood Pressure: Shifts in Hypertension Classification between Baseline and Post-baseline Value in Daytime Average Ambulatory Systolic Blood Pressure (mmHg) by Baseline Diabetic Status (All Data and Censored)	EXTS
14.3.4.3.1.4.1.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of Half-Hourly Ambulatory Systolic Blood Pressure (mmHg) and Time Matched Changes from Baseline by Visit and Half-Hourly Elapsed Time From ABPM Start (All Data and Censored)	EXTS
14.3.4.3.1.4.1.2	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of Half-Hourly Ambulatory Systolic Blood Pressure (mmHg) and Time Matched Changes from Baseline by Visit and Half-Hourly Elapsed Time From ABPM Start (All Data and Censored)	EXTS - ABPM Completers
14.3.4.3.1.4.2.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Blood Pressure: Summary of Half-Hourly Ambulatory Systolic Blood Pressure (mmHg) and Time Matched Changes from Baseline by Visit and Half-Hourly Clock Time Intervals (All Data and Censored)	EXTS

14.3.4.3.1.4.2.2	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Blood Pressure: Summary of Half-Hourly Ambulatory Systolic Blood Pressure (mmHg) and Time Matched Changes from Baseline by Visit and Half-Hourly Clock Time Intervals (All Data and Censored)	EXTS - ABPM Completers
14.3.4.3.1.4.3.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of 24-hour Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline at Day 120E and Day 180E by Total Daily Dose (All Data and Censored)	EXTS
14.3.4.3.1.4.3.2	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of Daytime Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline at Day 120E and Day 180E by Total Daily Dose (All Data and Censored)	EXTS
14.3.4.3.1.4.4.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of 24 Hour Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline at Day 120E by Day 90E Hemoglobin Tertiles (All Data and Censored)	EXTS
14.3.4.3.1.4.4.1.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of 24 Hour Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline at Day 120E by Day 90E Hemoglobin Tertiles and by Baseline Hypertensive Treatment Status (All Data and Censored)	EXTS
14.3.4.3.1.4.4.2	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of Daytime Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline at Day 120E by Day 90E Hemoglobin Tertiles (All Data and Censored)	EXTS
14.3.4.3.1.4.4.2.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of Daytime Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline at Day 120E by Day 90E Hemoglobin Tertiles and by Baseline Hypertensive Treatment Status (All Data and Censored)	EXTS
14.3.4.3.1.4.4.3	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of Nighttime Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline at Day 120E by Day 90E Hemoglobin Tertiles (All Data and Censored)	EXTS

14.3.4.3.1.4.4.3.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of Nighttime Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline at Day 120E by Day 90E Hemoglobin Tertiles and by Baseline Hypertensive Treatment Status(All Data and Cens ored)	EXTS
14.3.4.3.1.4.4.4	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of 24 Hour Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline at Day 180E by Day180E Hemoglobin Tertiles (All Data and Censored)	EXTS
14.3.4.3.1.4.4.4.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of 24 Hour Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline at Day 180E by Day180E Hemoglobin Tertiles and by Baseline Hypertensive Treatment Status (All Data and Censored)	EXTS
14.3.4.3.1.4.4.5	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of Daytime Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline at Day 180E by Day 180E Hemoglobin Tertiles (All Data and Censored)	EXTS
14.3.4.3.1.4.4.5.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of Daytime Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline at Day 180E by Day 180E Hemoglobin Tertiles and by Baseline Hypertensive Treatment Status (All Data and Censored)	EXTS
14.3.4.3.1.4.4.6	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of Nighttime Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline at Day 180E by Day 180E Hemoglobin Tertiles (All Data and Censored)	EXTS
14.3.4.3.1.4.4.6.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of Nighttime Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline at Day 180E by Day 180E Hemoglobin Tertiles and by Baseline Hypertensive Treatment Status(All Data and Censored)	EXTS

14.3.4.3.1.5.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of Visit 2E (Day 365) and Visit 7E (Day 1E) 24-hour Average Ambulatory Systolic Blood Pressure (mmHg)	EXTS – Continuing Subjects
14.3.4.3.1.5.2	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mixed Model Analysis of 24-hour Average Ambulatory Systolic Blood Pressure (mmHg) Comparing Visit 2E (Day 365) to Visit 7E (Day 1E)	EXTS – Continuing -Subjects
14.3.4.3.1.5.3	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of Visit 2E (Day 365) and Visit 7E (Day 1E) Daytime and Nighttime Average Ambulatory Systolic Blood Pressure (mmHg)	EXTS – Continuing Subjects
14.3.4.3.1.5.4	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mixed Model Analysis of Daytime and Nighttime Average Ambulatory Systolic Blood Pressure (mmHg) Comparing Visit 2E (Day 365) to Visit 7E (Day 1E)	EXTS – Continuing Subjects
14.3.4.3.1.4.5.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of 24 Hour Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline at Day 180E by Day 180E Hemoglobin Upper Limit of the Hgb Normal Range (All Data and Censored)	EXTS
14.3.4.3.1.4.5.2	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of Daytime Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline at Day 180E by Day 180E Hemoglobin Upper Limit of the Hgb Normal Range (All Data and Censored)	EXTS
14.3.4.3.1.4.5.3	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of Nighttime Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline at Day 180E by Day 180E Hemoglobin Upper Limit of the Hgb Normal Range (All Data and Censored)	EXTS
14.3.4.3.1.6.1.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of 24-hour Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline by Visit and History of Hypertension (All Data and Censored)	EXTS

14.3.4.3.1.6.1.2	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mixed Model Repeated Measures Analysis of 24-hour Average Ambulatory Systolic Blood Pressure (mmHg) by History of Hypertension (All Data and Censored)	EXTS
14.3.4.3.1.6.1.3	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of Daytime and Nighttime Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline by Visit and History of Hypertension (All Data and Censored)	EXTS
14.3.4.3.1.6.1.4	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mixed Model Repeated Measures Analysis of Daytime Average Ambulatory Systolic Blood Pressure (mmHg) by History of Hypertension (All Data and Censored)	EXTS
14.3.4.3.1.6.1.5	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mixed Model Repeated Measures Analysis of Nighttime Average Ambulatory Systolic Blood Pressure (mmHg) by History of Hypertension (All Data and Censored)	EXTS
14.3.4.3.1.6.2.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of 24-hour Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline by Visit and Baseline Diabetic Status (All Data and Censored)	EXTS
14.3.4.3.1.6.2.2	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mixed Model Repeated Measures Analysis of 24-hour Average Ambulatory Systolic Blood Pressure (mmHg) by Baseline Diabetic Status (All Data and Censored)	EXTS
14.3.4.3.1.6.2.3	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Summary of Daytime and Nighttime Average Ambulatory Systolic Blood Pressure (mmHg) and Change from Baseline by Visit and Baseline Diabetic Status (All Data and Censored)	EXTS
14.3.4.3.1.6.2.4	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mixed Model Repeated Measures Analysis of Daytime Average Ambulatory Systolic Blood Pressure (mmHg) by Baseline Diabetic Status (All Data and Censored)	EXTS

14.3.4.3.1.6.2.5	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mixed Model Repeated Measures Analysis of Nighttime Average Ambulatory Systolic Blood Pressure (mmHg) by Baseline Diabetic Status (All Data and Censored)	EXTS
14.3.4.3.1.6.2.6	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: ANCOVA of Change in 24-hour Average Ambulatory Systolic Blood Pressure (mmHg) as a Funtion of Baseline systolic Blood Pressure, Baseline Diabetic Status, Dose, Age,Weight, and Baseline Hypertensive Treatment Status by Visit 12E (Day 120E) and 14E (Day 180E)	EXTS
14.3.4.3.2.1.1.1.1	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Summary of 24-hour Average Ambulatory Diastolic Blood Pressure (mmHg) and Change from Baseline by Visit (All Data and Censored)	EXTS
14.3.4.3.2.1.1.1.2	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Mixed Model Repeated Measures Analysis of in 24-hour Average Ambulatory Diastolic Blood Pressure (mmHg) (All Data and Censored)	EXTS
14.3.4.3.2.1.1.1.3	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Mixed Model Repeated Measures Analysis of 24-hour Average Ambulatory Diastolic Blood Pressure (mmHg) (All Data and Censored): Sensitivity Analysis (ABPM Completers)	EXTS - ABPM Completers
14.3.4.3.2.1.1.2.1	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Summary of Daytime and Nighttime Average Ambulatory Diastolic Blood Pressure (mmHg) and Change from Baseline by Visit (All Data and Censored)	EXTS
14.3.4.3.2.1.1.2.2	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Mixed Model Repeated Measures Analysis of Daytime Average Ambulatory Diastolic Blood Pressure (mmHg) (All Data and Censored)	EXTS
14.3.4.3.2.1.1.2.3	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Mixed Model Repeated Measures Analysis of Daytime Average Ambulatory Diastolic Blood Pressure (mmHg) (All Data and Censored): Sensitivity Analysis (ABPM Completers)	EXTS - ABPM Completers
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14.3.4.1.2.2.5	eDISH Plot of MRS-TU-2019 Peak Post-baseline Total Bilirubin vs. Peak Post-baseline AST by Treatment Group – Log-Log Scale	SS
14.3.4.1.2.2.6	eDISH Plot of MRS-TU-2020 Peak Post-baseline Total Bilirubin vs. Peak Post-baseline ALT by Treatment Group – Log-Log Scale	SS
14.3.4.1.5.1.1	MRS-TU-2019EXT Lipid Panel: Mean (+/- SE) Triglyceride and LDL Profiles	EXTS
14.3.4.1.5.1.2	MRS-TU-2019EXT Lipid Panel: Mean (+/- SE) Triglyceride and LDL Profiles	SS
14.3.4.2.1.1.1.2	MRS-TU-2019EXT Mean (+/- SE) Morning Time 0 In Clinic Predose Blood Pressure Profiles (All Data and Censored)	EXTS

14.3.4.2.1.1.1.3	MRS-TU-2019EXT Mean (+/- SE) Change from Baseline In Clinic Time 0 Blood Pressure Profiles (All Data and Censored)	EXTS
14.3.4.2.1.1.1.4	MRS-TU-2019EXT Box Plot of Time 0 Systolic Blood Pressure Overlaying Visit (All Data and Censored)	EXTS
14.3.4.2.1.1.1.5	MRS-TU-2019EXT Box Plot of Time 0 In Clinic Diastolic Blood Pressure Overlaying Visit (All Data and Censored)	EXTS
14.3.4.2.1.1.1.6	MRS-TU-2019EXT Cumulative Distribution Curve of Time 0 In Clinic Blood Pressure Overlaying Visit (All Data and Censored)	EXTS
14.3.4.2.1.4.1	MRS-TU-2019EXT Kaplan Meier Plot of the Days from Baseline to the First Occurrence of Stage 1 Hypertensive Event (All Data and Censored)	EXTS
14.3.4.2.1.4.2	MRS-TU-2019EXT Kaplan Meier Plot of the Days from Baseline to the First Occurrence of Stage 2 Hypertensive Event (All Data and Censored)	EXTS
14.3.4.2.1.4.3	MRS-TU-2019EXT Kaplan Meier Plot of the Days from Baseline to the First Occurrence of Stage 1 Hypertensive Event with Confirmatory Events (All Data and Censored)	EXTS
14.3.4.2.1.4.4	MRS-TU-2019EXT Kaplan Meier Plot of the Days from Baseline to the First Occurrence of Stage 2 Hypertensive Event with Confirmatory Events (All Data and Censored)	EXTS
14.3.4.2.1.4.5	MRS-TU-2019EXT SOV Kaplan Meier Plot of the Days from Baseline to the First Occurrence of Stage 1 Hypertensive Event with Confirmatory Events Overlaying Baseline Hypertensive Status (All Data and Censored)	EXTS
14.3.4.2.1.4.6	MRS-TU-2019EXT Kaplan Meier Plot of the Days from Baseline to the First Occurrence of Stage 2 Hypertensive Event with Confirmatory Events Overlaying Baseline Hypertensive Status (All Data and Censored)	EXTS
14.3.4.2.1.5.1.1	MRS-TU-2019EXT Scatter Plot of Time 0 In Clinic Systolic Blood Pressure at Visit 6E versus 24-Hour Average Ambulatory Systolic Blood Pressure at Visit 7E (Day 1E) (All Data and Censored)	EXTS

14.3.4.2.1.5.1.2	MRS-TU-2019EXT Scatter Plot of Time 0 In Clinic Systolic Blood Pressure at Visit 6E versus Daytime Average Ambulatory Systolic Blood Pressure at Visit 7E (All Data and Censored)	EXTS
14.3.4.2.1.5.2.1	MRS-TU-2019EXT Scatter Plot of Time 0 In Clinic Systolic Blood Pressure at Visit 13E versus 24-Hour Average Ambulatory Systolic Blood Pressure at Visit 14E (All Data and Censored)	EXTS
14.3.4.2.1.5.2.2	MRS-TU-2019EXT Scatter Plot of Time 0 In Clinic Systolic Blood Pressure at Visit 13E versus Daytime Average Ambulatory Systolic Blood Pressure at Visit 14E (All Data and Censored)	EXTS
14.3.4.2.1.5.3.1	MRS-TU-2019EXT Scatter Plot of Time 0 In Clinic Systolic Blood Pressure at Visit 15E versus 24-Hour Average Ambulatory Systolic Blood Pressure at Visit 16E (All Data and Censored)	EXTS
14.3.4.2.1.5.3.2	MRS-TU-2019EXT Scatter Plot of Time 0 In Clinic Systolic Blood Pressure at Visit 15E versus Daytime Average Ambulatory Systolic Blood Pressure at Visit 16E (All Data and Censored)	EXTS
14.3.4.2.1.5.4.1	MRS-TU-2019EXT Scatter Plot of Time 0 In Clinic Diastolic Blood Pressure at Visit 6E versus 24-Hour Average Ambulatory Diastolic Blood Pressure at Visit 7E (All Data and Censored)	EXTS
14.3.4.2.1.5.4.2	MRS-TU-2019EXT Scatter Plot of Time 0 In Clinic Diastolic Blood Pressure at Visit 6E versus Daytime Average Ambulatory Diastolic Blood Pressure at Visit 7E (All Data and Censored)	EXTS
14.3.4.2.1.5.5.1	MRS-TU-2019EXT Scatter Plot of In Clinic Time 0 Diastolic Blood Pressure at Visit 13E versus 24-Hour Average Ambulatory Diastolic Blood Pressure at Visit 14E (All Data and Censored)	EXTS
14.3.4.2.1.5.5.2	MRS-TU-2019EXT Scatter Plot of Time 0 In Clinic Diastolic Blood Pressure at Visit 13E versus Daytime Average Ambulatory Diastolic Blood Pressure at Visit 14E (All Data and Censored)	EXTS
14.3.4.2.1.5.6.1	MRS-TU-2019EXT Scatter Plot of Time 0 In Clinic Diastolic Blood Pressure at Visit 15E versus 24-Hour Average Ambulatory Diastolic Blood Pressure at Visit 16E (All Data and Censored)	EXTS

14.3.4.2.1.5.6.2	MRS-TU-2019EXT Scatter Plot of Time 0 In Clinic Diastolic Blood Pressure at Visit 15E versus Daytime Average Ambulatory Diastolic Blood Pressure at Visit 16E (All Data and Censored)	EXTS
14.3.4.2.1.6.1.1	MRS-TU-2019EXT Scatter Plot of Change from Baseline Time 0 In Clinic Systolic Blood Pressure at Visit 13E versus 24-Hour Average Change from Baseline in Ambulatory Systolic Blood Pressure at Visit 14E (All Data and Censored)	EXTS
14.3.4.2.1.6.1.2	MRS-TU-2019EXT Scatter Plot of Change from Baseline Time 0 In Clinic Systolic Blood Pressure at Visit 13E versus Daytime Average Change from Baseline in Ambulatory Systolic Blood Pressure at Visit 14E (All Data and Censored)	EXTS
14.3.4.2.1.6.2.1	MRS-TU-2019EXT Scatter Plot of Change from Baseline Time 0 In Clinic Systolic Blood Pressure at Visit 15E versus 24-Hour Average Change from Baseline in Ambulatory Systolic Blood Pressure at Visit 16E (All Data and Censored)	EXTS
14.3.4.2.1.6.2.2	MRS-TU-2019EXT Scatter Plot of Change from Baseline Time 0 In Clinic Systolic Blood Pressure at Visit 15E versus Daytime Average Change from Baseline in Ambulatory Systolic Blood Pressure at Visit 16E (All Data and Censored)	EXTS
14.3.4.2.1.6.3.1	MRS-TU-2019EXT Scatter Plot of Change from Baseline Time 0 In Clinic Diastolic Blood Pressure at Visit 13E versus 24-Hour Average Change from Baseline in Ambulatory Diastolic Blood Pressure at Visit 14E (All Data and Censored)	EXTS
14.3.4.2.1.6.3.2	MRS-TU-2019EXT Scatter Plot of Change from Baseline Time 0 In Clinic Diastolic Blood Pressure at Visit 13E versus Daytime Average Change from Baseline in Ambulatory Diastolic Blood Pressure at Visit 14E (All Data and Censored)	EXTS
14.3.4.2.1.6.4.1	MRS-TU-2019EXT Scatter Plot of Change from Baseline Time 0 In Clinic Diastolic Blood Pressure at Visit 15E versus 24-Hour Average Change from Baseline in Ambulatory Diastolic Blood Pressure at Visit 16E (All Data and Censored)	EXTS
14.3.4.2.1.6.4.2	MRS-TU-2019EXT Scatter Plot of Change from Baseline Time 0 In Clinic Diastolic Blood Pressure at Visit 15E versus Daytime Average Change from Baseline in Ambulatory Diastolic Blood Pressure at Visit 16E (All Data and Censored)	EXTS

14.3.4.2.1.7.2	MRS-TU-2019EXT Box Plot of Time 0 In Clinic Systolic Blood Pressure by MRS-TU-2019 Treatment Group Overlaying Washout Visit (All Data and Censored)	All Continuing SOV Subjects
14.3.4.2.1.7.3	MRS-TU-2019EXT Box Plot of Time 0 Diastolic Blood Pressure by MRS-TU-2019 Treatment Group Overlaying Washout Visit (All Data and Censored)	All Continuing SOV Subjects
14.3.4.2.2.2.1	MRS-TU-2019 Mean (+/- SE) Time 0 In Clinic Fasting Blood Pressure Profiles Overlaying Treatment Group (All Data and Censored)	SS
14.3.4.2.2.2.2	MRS-TU-2019 Mean (+/- SE Change from Baseline Time 0 In Clinic Fasting Blood Pressure Profiles Overlaying Treatment Group (All Data and Censored)	SS
14.3.4.2.2.2.3	MRS-TU-2019 Mean (+/- SE) Change from Baseline Time 0 In Clinic Vital Signs for Fasting Visits Overlaying Baseline Hypertension Classification by Treatment Group (All Data and Censored)	SS
14.3.4.2.2.4.2.1	Cumulative Distribution Curve of Change from Baseline in 24-Hour Mean In Clinic Systolic Blood Pressure Overlaying Visit for MRS-TU-2019 SOV2012-F1 Group (All Data and Censored)	SS
14.3.4.2.2.4.2.2	Histogram of Categorical Change from Baseline to Visit 4 (Day 14) in 24-Hour Mean In Clinic Systolic Blood Pressure for MRS-TU-2019 SOV2012-F1 Group (All Data and Censored)	SS
14.3.4.2.2.4.2.3	Histogram of Categorical Change from Baseline to Visit 6 (Day 42) in 24-Hour Mean In Clinic Systolic Blood Pressure for MRS-TU-2019 SOV2012-F1 Group (All Data and Censored)	SS
14.3.4.2.2.4.2.4	Histogram of Categorical Change from Baseline to Visit 8 (Day 90) in 24-Hour Mean In Clinic Systolic Blood Pressure for MRS-TU-2019 Overlaying Treatment Group (All Data and Censored)	SS
14.3.4.2.2.4.2.5	Cumulative Distribution Curve of Change from Baseline in 24-Hour Mean In Clinic Diastolic Blood Pressure Overlaying Visitfor MRS-TU-2019 SOV2012-F1 Group (All Data and Censored)	SS
14.3.4.2.2.4.2.6	Histogram of Categorical Change from Baseline to Visit 4 (Day 14) in 24-Hour Mean In Clinic Diastolic Blood Pressure for MRS-TU-2019 SOV2012-F1 Group (All Data and Censored)	SS

14.3.4.2.2.4.2.7	Histogram of Categorical Change from Baseline to Visit 6 (Day 42) in 24-Hour Mean In Clinic Diastolic Blood Pressure for MRS-TU-2019 SOV2012-F1 Group (All Data and Censored)	SS
14.3.4.2.2.4.2.8	Histogram of Categorical Change from Baseline to Visit 8 (Day 90) in 24-Hour Mean In Clinic Diastolic Blood Pressure for MRS-TU-2019 Overlaying Treatment Group (All Data and Censored)	SS
14.3.4.2.2.6.1	MRS-TU-2019 Kaplan Meier Plot of the Days from Baseline to the First Occurrence of Stage 1 Hypertensive Event by Treatment Group (All Data and Censored)	SS
14.3.4.2.2.6.2	MRS-TU-2019 Kaplan Meier Plot of the Days from Baseline to the First Occurrence of Stage 2 Hypertensive Event by Treatment Group (All Data and Censored)	SS
14.3.4.2.2.6.3	MRS-TU-2019 Kaplan Meier Plot of the Days from Baseline to the First Occurrence of Stage 1 Hypertensive Event with Confirmatory Events by Treatment Group (All Data and Censored)	SS
14.3.4.2.2.6.4	MRS-TU-2019 Kaplan Meier Plot of the Days from Baseline to the First Occurrence of Stage 2 Hypertensive Event with Confirmatory Events by Treatment Group (All Data and Censored)	SS
14.3.4.2.2.6.5	MRS-TU-2019 Kaplan Meier Plot of the Days from Baseline to the First Occurrence of Stage 1 Hypertensive Event with Confirmatory Events Overlaying Baseline Hypertensive Status in SOV2012-F1 Treated Subjects (All Data and Censored)	SS
14.3.4.2.1.6.6	MRS-TU-2019 Kaplan Meier Plot of the Days from Baseline to the First Occurrence of Stage 2 Hypertensive Event with Confirmatory Events Overlaying Baseline Hypertensive Status in SOV2012-F1 Treated Subjects(All Data and Censored)	SS
14.3.4.2.1.6.7	MRS-TU-2019 Kaplan Meier Plot of the Days from Baseline to the First Occurrence of Stage 1 Hypertensive Event with Confirmatory Events Overlaying Baseline Hypertensive Status in Androgel Treated Subjects (All Data and Censored)	SS
14.3.4.2.1.6.8	MRS-TU-2019 Kaplan Meier Plot of the Days from Baseline to the First Occurrence of Stage 2 Hypertensive Event with Confirmatory Events Overlaying Baseline Hypertensive Status in Androgel Treated Subjects(All Data and Censored)	SS

14.3.4.2.2.7.1	Plot of In Clinic Mean Systolic Blood Pressure and Mean Plasma T Concentration vs. Time for MRS-TU-2019 SOV2012-F1 Group by Visit (All Data and Censored)	PKS
14.3.4.2.2.7.2	Plot of In Clinic Mean Diastolic Blood Pressure and Mean Plasma T Concentration vs. Time for MRS-TU-2019 SOV2012-F1 Group by Visit (All Data and Censored)	PKS
14.3.4.2.2.7.3	Plot of In Clinic Mean Heart Rate and Mean Plasma T Concentration vs. Time for MRS-TU-2019 SOV2012-F1 Group by Visit (All Data and Censored)	PKS
14.3.4.2.2.7.4	Plot of In Clinic Mean Systolic Blood Pressure and Mean Plasma T Concentration vs. Time at Visit 8 (Day 90) for MRS-TU-2019 AndroGel Group (All Data and Censored)	PKS
14.3.4.2.2.7.5	Plot of In Clinic Mean Diastolic Blood Pressure and Mean Plasma T Concentration vs. Time at Visit 8 (Day 90) for MRS-TU-2019 AndroGel Group (All Data and Censored)	PKS
14.3.4.2.2.7.6	Plot of Mean Heart Rate and Mean Plasma T Concentration vs. Time at Visit 8 (Day 90) for MRS-TU-2019 AndroGel (All Data and Censored)	PKS
14.3.4.3.1.1.2.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Box Plot of 24-hour Average Ambulatory Systolic Blood Pressure Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.1.1.2.2	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Box Plot of Daytime Average Ambulatory Systolic Blood Pressure Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.1.1.2.3	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Box Plot of Nighttime Average Ambulatory Systolic Blood Pressure Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.1.1.3.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Cumulative Distribution Curve of 24-hour Average Ambulatory Systolic Blood Pressure Overlaying Visit (All Data and Censored)	EXTS

14.3.4.3.1.1.3.2	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Cumulative Distribution Curve of Daytime Average Ambulatory Systolic Blood Pressure Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.1.1.3.3	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Cumulative Distribution Curve of Nighttime Average Ambulatory Systolic Blood Pressure Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.1.1.4.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Forest Plot of Least Squares Mean Differences (95% CIs) Between Visits in 24-hour Average Ambulatory Systolic Blood Pressure (mmHg) (All Data and Censored)	EXTS
14.3.4.3.1.1.4.2	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Forest Plot of Least Squares Mean Differences (95% CIs) Between Visits in Daytime Average Ambulatory Systolic Blood Pressure (mmHg) (All Data and Censored)	EXTS
14.3.4.3.1.1.4.3	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Forest Plot of Least Squares Mean Differences (95% CIs) Between Visits in Nighttime Average Ambulatory Systolic Blood Pressure (mmHg) (All Data and Censored)	EXTS
14.3.4.3.1.2.3	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Cumulative Distribution Curve of Categorical Change from Baseline Overlaying Visit 14E (Day 120E) and Visit 16E (Day 180E) in 24-hour Average Ambulatory Systolic Blood Pressure (All Data and Censored)	EXTS
14.3.4.3.1.2.4	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Histogram of Categorical Change from Baseline to Visit 14E (Day 120E) in 24-hour Average Ambulatory Systolic Blood Pressure (All Data and Censored)	EXTS
14.3.4.3.1.2.5	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Histogram of Categorical Change from Baseline to Visit 16E (Day 180E) in 24-hour Average Ambulatory Systolic Blood Pressure (All Data and Censored)	EXTS

14.3.4.3.1.4.1.3	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mean Half-Hourly Ambulatory Systolic Blood Pressure by Half-Hourly Elapsed Time From ABPM Start Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.1.4.1.4	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mean Half-Hourly Ambulatory Systolic Blood Pressure by Half-Hourly Elapsed Time From ABPM Start Overlaying Visit (All Data and Censored)	EXTS - ABPM Completers
14.3.4.3.1.4.1.5	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mean Half-Hourly Time Matched Changes from Baseline in Ambulatory Systolic Blood Pressure by Half-Hourly Elapsed Time From ABPM Start Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.1.4.1.6	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mean Half-Hourly Time Matched Changes from Baseline in Ambulatory Systolic Blood Pressure by Half-Hourly Elapsed Time From ABPM Start Overlaying Visit (All Data and Censored)	EXTS - ABPM Completers
14.3.4.3.1.4.2.3	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mean Half-Hourly Ambulatory Systolic Blood Pressure by Half-Hourly Clock Time Intervals Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.1.4.2.4	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mean Half-Hourly Ambulatory Systolic Blood Pressure by Half-Hourly Clock Time Intervals Overlaying Visit (All Data and Censored)	EXTS - ABPM Completers
14.3.4.3.1.4.2.5	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mean Half-Hourly Time Matched Changes from Baseline in Ambulatory Systolic Blood Pressure by Half-Hourly Clock Time Intervals Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.1.4.2.6	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Mean Half-Hourly Time Matched Changes from Baseline in Ambulatory Systolic Blood Pressure by Half-Hourly Clock Time Intervals Overlaying Visit (All Data and Censored)	EXTS - ABPM Completers

14.3.4.3.1.4.3.1	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Box Plot of 24-hour Average Ambulatory Systolic Blood Pressure Overlaying Dose- Visit 14E (All Data and Censored)	EXTS
14.3.4.3.1.4.3.2	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Box Plot of 24-hour Average Ambulatory Systolic Blood Pressure Overlaying Dose- Visit 16E (All Data and Censored)	EXTS
14.3.4.3.1.4.3.3	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Box Plot of Daytime Average Ambulatory Systolic Blood Pressure Overlaying Dose- Visit 14E (All Data and Censored)	EXTS
14.3.4.3.1.4.3.4	Primary MRS-TU-2019EXT ABPM Parameter Ambulatory Systolic Blood Pressure: Box Plot of Daytime Average Ambulatory Systolic Blood Pressure Overlaying Dose- Visit 16E (All Data and Censored)	EXTS
14.3.4.3.2.1.2.1	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Box Plot of 24-hour Average Ambulatory Diastolic Blood Pressure Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.2.1.2.2	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Box Plot of Daytime Average Ambulatory Diastolic Blood Pressure Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.2.1.2.3	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Box Plot of Nighttime Average Ambulatory Diastolic Blood Pressure Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.2.1.3.1	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Cumulative Distribution Curve of 24-hour Average Ambulatory Diastolic Blood Pressure Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.2.1.3.2	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Cumulative Distribution Curve of Daytime Average Ambulatory Diastolic Blood Pressure Overlaying Visit (All Data and Censored)	EXTS

14.3.4.3.2.1.3.3	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Cumulative Distribution Curve of Nighttime Average Ambulatory Diastolic Blood Pressure Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.2.1.4.1	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Forest Plot of Least Squares Mean Differences (95% CIs) Between Visits in 24-hour Average Ambulatory Diastolic Blood Pressure (mmHg) (All Data and Censored)	EXTS
14.3.4.3.2.1.4.2	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Forest Plot of Least Squares Mean Differences (95% CIs) Between Visits in Daytime Average Ambulatory Diastolic Blood Pressure (mmHg) (All Data and Censored)	EXTS
14.3.4.3.2.1.4.3	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Forest Plot of Least Squares Mean Differences (95% CIs) Between Visits in Nighttime Average Ambulatory Diastolic Blood Pressure (mmHg) (All Data and Censored)	EXTS
14.3.4.3.2.2.3	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure:Cumulative Distribution Curve of Change from Baseline Overlaying Visit 14E (Day 120E) and Visit 16E (Day 180E) in 24-hour Average Ambulatory Diastolic Blood Pressure (All Data and Censored)	EXTS
14.3.4.3.2.2.4	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Histogram of Categorical Change from Baseline to Visit 14E (Day 120E) in 24-hour Average Ambulatory Diastolic Blood Pressure (All Data and Censored)	EXTS
14.3.4.3.2.2.5	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Histogram of Categorical Change from Baseline to Visit 16E (Day 180E) in 24-hour Average Ambulatory Diastolic Blood Pressure (All Data and Censored)	EXTS
14.3.4.3.2.4.1.3	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Mean Half-Hourly Ambulatory Diastolic Blood Pressure by Half-Hourly Elapsed Time From ABPM Start Overlaying Visit (All Data and Censored)	EXTS

14.3.4.3.2.4.1.4	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Mean Half-Hourly Ambulatory Diastolic Blood Pressure by Half-Hourly Elapsed Time From ABPM Start Overlaying Visit (All Data and Censored)	EXTS - ABPM Completers
14.3.4.3.2.4.1.5	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Mean Half-Hourly Time Matched Changes from Baseline in Ambulatory Diastolic Blood Pressure by Half-Hourly Elapsed Time From ABPM Start Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.2.4.1.6	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Mean Half-Hourly Time Matched Changes from Baseline in Ambulatory Diastolic Blood Pressure by Half-Hourly Elapsed Time From ABPM Start Overlaying Visit (All Data and Censored)	EXTS - ABPM Completers
14.3.4.3.2.4.2.3	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Mean Half-Hourly Ambulatory Diastolic Blood Pressure by Half-Hourly Clock Time Intervals Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.2.4.2.4	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Mean Half-Hourly Ambulatory Diastolic Blood Pressure by Half-Hourly Clock Time Intervals Overlaying Visit (All Data and Censored)	EXTS - ABPM Completers
14.3.4.3.2.4.2.5	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Mean Half-Hourly Time Matched Changes from Baseline in Ambulatory Diastolic Blood Pressure by Half-Hourly Clock Time Intervals Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.2.4.2.6	MRS-TU-2019EXT ABPM Parameter Ambulatory Diastolic Blood Pressure: Mean Half-Hourly Time Matched Changes from Baseline in Ambulatory Diastolic Blood Pressure by Half-Hourly Clock Time Intervals Overlaying Visit (All Data and Censored)	EXTS - ABPM Completers
14.3.4.3.3.1.3	MRS-TU-2019EXT ABPM Parameter Ambulatory Heart Rate: Box Plot of 24-hour Average Ambulatory Heart Rate Overlaying Visit (All Data and Censored)	EXTS

14.3.4.3.3.1.4	MRS-TU-2019EXT ABPM Parameter Ambulatory Heart Rate: Forest Plot of Least Squares Mean Differences (95% CIs) Between Visits in 24-hour Average Ambulatory Heart Rate (bpm) (All Data and Censored)	EXTS
14.3.4.3.3.2.1.2	MRS-TU-2019EXT ABPM Parameter Ambulatory Heart Rate: Mean Half-Hourly Ambulatory Heart Rate by Half-Hourly Elapsed Time From ABPM Start Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.3.2.1.3	MRS-TU-2019EXT ABPM Parameter Ambulatory Heart Rate: Mean Half-Hourly Time Matched Changes from Baseline in Ambulatory Heart Rate by Half-Hourly Elapsed Time From ABPM Start Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.3.2.2.2	MRS-TU-2019EXT ABPM Parameter Ambulatory Heart Rate: Mean Half-Hourly Ambulatory Heart Rate by Half-Hourly Clock Time Intervals Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.3.2.2.3	MRS-TU-2019EXT ABPM Parameter Ambulatory Heart Rate: Mean Half-Hourly Time Matched Changes from Baseline in Ambulatory Heart Rate by Half-Hourly Clock Time Intervals Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.4.1.2	MRS-TU-2019EXT ABPM Parameter Ambulatory Mean Arterial Pressure: Box Plot of 24-hour Average Ambulatory Mean Arterial Pressure Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.4.1.3	MRS-TU-2019EXT ABPM Parameter Ambulatory Mean Arterial Pressure: Cumulative Distribution Curve of 24-hour Average Ambulatory Mean Arterial Pressure Overlaying Visit (All Data and Censored)	EXTS
14.3.4.3.4.1.4	MRS-TU-2019EXT ABPM Parameter Ambulatory Mean Arterial Pressure: Forest Plot of Least Squares Mean Differences (95% CIs) Between Visits in 24-hour Average Ambulatory Mean Arterial Pressure (mmHg) (All Data and Censored)	EXTS
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16.2. DERIVATION OF TITRATION ALGORITHM FOR SOV2012-F1 (TESTOSTERONE UNDECANOATE 200 MG) AND OPTIMIZATION OF TITRATION CUT-OFFS FOR EXTENSION STUDY

Introduction:

To minimize unnecessary exposure to higher than needed testosterone concentrations at the initiation of therapy, the MRS-TU-2019EXT (ABPM) study started all subjects on a lower starting dose of 400 mg daily (200mg a.m. dose, 200mg p.m. dose) than the 600 mg daily dose used in the MRS-TU-2019 study (400mg a.m. dose, 200mg p.m. dose). Visit 4 and Visit 6 refer to the PK visits used to determine dose adjustments at Visits 5 and 7 in MRS-TU-2019. Note that in MRS-TU-2019EXT, the PK data for dose titration is obtained at Visits 8E and 10E, with dose titration occurring at Visits 9E and 11E.

Methods:

Marius has carried out PK modeling and concordance simulations based on the 90-day efficacy results from MRS-TU-2019 (total 196 observed subjects data) for determining the optimum sampling window for titration decision.

Nonparametric superposition method was performed for modeling and simulation using a validated Phoenix WinNonLin software ver6.4 (Certara, NJ, USA). For the 196 observed data from Phase III MRS-TU-2019 study, morning (0-12 hour) and evening (12-24 hour) PK concentrations were used separately to model and simulate PK profiles for lower starting dose in morning (200mg a.m.) or evening 200mg p.m. at Visit 4; and simulated morning concentrations were combined with evening concentrations to obtain simulated 24-hour PK profile. In total 138 subjects' data were converged on nonparametric superposition approach, and used for further simulations. An increment/decrement scale of 100mg/100mg were applied for the two opportunities of dose titrations at visit 5 (visit 9E in MRS-TU2019EXT) and visit 7 (visit 11E in MRS-TU2019EXT), respectively.

Trials with various cutoff combinations for up- and down-titrations were simulated, including cutoffs of 235, 300, 350, 400 and 450 ng/dL for up-titration as well as 800, 900, 1000, and 1120 ng/dL for down-titration. With simulated profiles for visit 4, each simulated subject concentrations at a randomly selected postdose timepoint (from C3, or C4 or C5; randomization code generated in excel) was evaluated to make titration decisions.

Subsequently, visit 6 PK concentrations were simulated based on the doses after titrations from visit 4, and the same rules (cutoffs) for titration decisions were applied again on simulated visit 6. After second opportunity for up-, down-, or no-titration on simulated visit 6 results, visit 8 PK concentrations were in turn simulated to generate PK profiles for efficacy phase. The primary and secondary efficacy endpoints as well as the performance of titration algorithm (titration concordance analysis) were evaluated based on simulated results from visit 4 (first titration visit), visit 6 (second titration visit), and visit 8 (efficacy phase). (Refer to Section 4.1 for primary and secondary efficacy endpoints; and Section 9.5 for titration algorithm concordance analysis).

While the MRS-TU-2019 study used a window from 3 to 5 hours post-morning dose, the simulations also tested the effect of sampling 6 hours post-dose. After the identification of best titration cutoffs (400-900 ng/dL) for 200mg a.m./200mg p.m. starting dose, the same approaches were also utilized for modeling and simulations to test randomly selected C4, or C5 or C6 for titration decisions based on 400-900 ng/dL cutoffs. The primary and secondary efficacy endpoints as well as the concordance analysis were also analyzed.

Results:

These simulations used a normal range of 252 to 840 ng/dL (derived from a serum normal range of 300 to 1000 ng/dL with a factor of 0.84 for NaF/EDTA plasma samples).

1) New cutoffs for titration decisions

Up-titration cutoff optimization:

We tested multiple up- and down-titration cutoff combinations for simulations, and primary and secondary efficacy results were analyzed based on these simulations. As shown in following Table , up-titration of 235 and 300 in combination with 1120 down-titration cutoff will likely result in unmet primary efficacy endpoint (percent of T Cavg within normal range < 75%). And from Table , combination of 350-1120 or 450-800 may have the risk of not meeting secondary efficacy endpoint (percent of C_{max} within the range of 1512-2100 from the x0.84 scaled of FDA range 1500-1800 ng/dL > 5%). Therefore, 400 ng/dL appears to be an appropriate selection for up-titration cutoff, while we further optimized down-titration cutoffs in the next step. Different sample sizes used in Table and Table are due to these simulations being run at different times during the course of MRS-TU-2019, and thus the data set available for running the simulations grew as the study progressed.

Table 12 Primary Efficacy Endpoints (Normal Range: 252-840 ng/dL) on different cutoff combinations

	FDA Target	SOV2012-F1 N=92	SOV2012-F1 N=86	SOV2012-F1 N=86	SOV2012-F1 N=133	SOV2012-F1 N=133
T C_{avg}	≥ 75%	69.6%	75.6%	83.7%	88.7%	90.2%
Cutoffs:	*Up*	*235*	*300*	*350*	*400*	*450*
(ng/dL)	*Down*	*1120*	*1120*	*1120*	*800*	*800*

Table 13 Secondary Efficacy Endpoints on different cutoff combinations

C_{max} Category (ng/dL)	FDA Target	SOV2012-F1 N=92	SOV2012-F1 N=86	SOV2012-F1 N=86	SOV2012-F1 N=133	SOV2012-F1 N=133
≤1260	≥ 85%	91.3%	89.5%	87.2%	86.5%	81.2%
1512-2100	≤ 5%	3.3%	3.5%	4.7%	3.8%	4.5%

≥2100	0	1.1% (N=1)	2.3% (N=2)	2.3% (N=2)	3.0% (N=4)	3.8% (N=5)
Cutoffs	*Up*	*235*	*300*	*350*	*400*	*450*
(ng/dL):	*Down*	*1120*	*1120*	*1120*	*800*	*800*

Further optimization for down-titration cutoff:

After identification of 400 ng/dL as the up-titration cutoff, we further optimized down-titration cutoffs by comparing combinations of 400-800, 400-900, 400-950 and 400-1000 ng/dL. As shown in Table , 400-900, 400-950 and 400-1000 had better primary efficacy results than 400-800 combinations having over 90% of T C_{avg} within normal range.

In addition, from secondary efficacy results in Table , the cutoffs of 400-950 or 400-1000 may have the risk of not meeting secondary efficacy endpoint (percent of C_{max} within the range of 1512-2100 from the x0.84 scaled of FDA range 1500-1800 ng/dL > 5%).

The conclusion based on simulated results using the PK data and taking into account the both the primary (C_{avg}) and secondary (C_{max}) objectives 400-900 ng/dL appears to be the optimized up- and down-titration cutoffs for MRS-TU-2019EXT on starting dose of 200mg a.m./200mg p.m..

Table 14 Primary Efficacy Endpoints (Normal Range: 252-840 ng/dL) on additional cutoff combinations

	FDA Target	SOV2012-F1 N=138	SOV2012-F1 N=138	SOV2012-F1 N=138	SOV2012-F1 N=138
T C_{avg}	≥ 75%	87.7%	90.6%	91.3%	91.3%
Cutoffs:	*Up*	*400*	400	*400*	*400*
(ng/dL)	*Down*	*800*	900	*950*	*1000*

Table 15 Secondary Efficacy Endpoints on additional cutoff combinations using scaled C_{max} categories

C_{max} Category (ng/dL)	FDA Target	SOV2012-F1 N=138	SOV2012-F1 N=138	SOV2012-F1 N=138	SOV2012-F1 N=138
≤1260	≥ 85%	86.2%	84.8%	84.8%	84.1%
1512-2100	≤ 5%	3.6%	4.3%	4.3%	5.1%
≥2100	0	2.9% (N=4)	2.9%(N=4)	2.9%(N=4)	2.9%(N=4)
Cutoffs	*Up*	*400*	**400**	*400*	*400*
(ng/dL):	*Down*	*800*	**900**	*950*	*1000*

Table 16 Secondary Efficacy Endpoints on additional cutoff combinations using unscaled C_{max} categories

C_{max} Category (ng/dL)	FDA Target	SOV2012-F1 N=138	SOV2012-F1 N=138	SOV2012-F1 N=138	SOV2012-F1 N=138
≤1500	≥ 85%	92.8%	92.0%	92.0%	91.3%
1800-2500	≤ 5%	3.6%	3.6%	3.6%	3.6%
≥2500	0	0 (N=0)	0 (N=0)	0 (N=0)	0 (N=0)
Cutoffs	*Up*	*400*	**400**	*400*	*400*
(ng/dL):	*Down*	*800*	**900**	*950*	*1000*

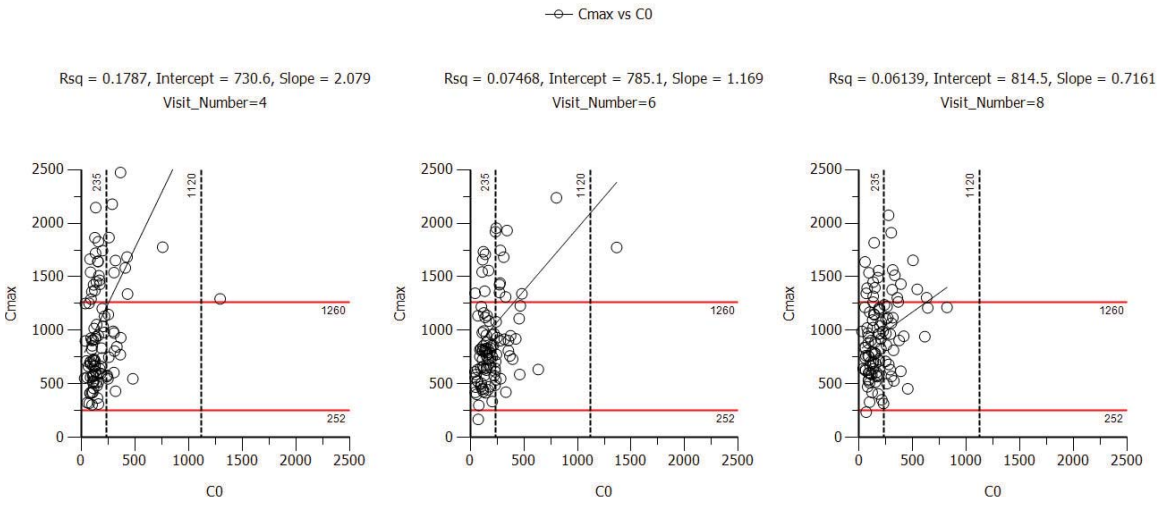
2) Concordance analysis on simulated results

Correlation of C_{max} vs. Concentration at x hours after morning dose (C_x) (Scatterplots) on Phase III MRS-TU2019 study data:

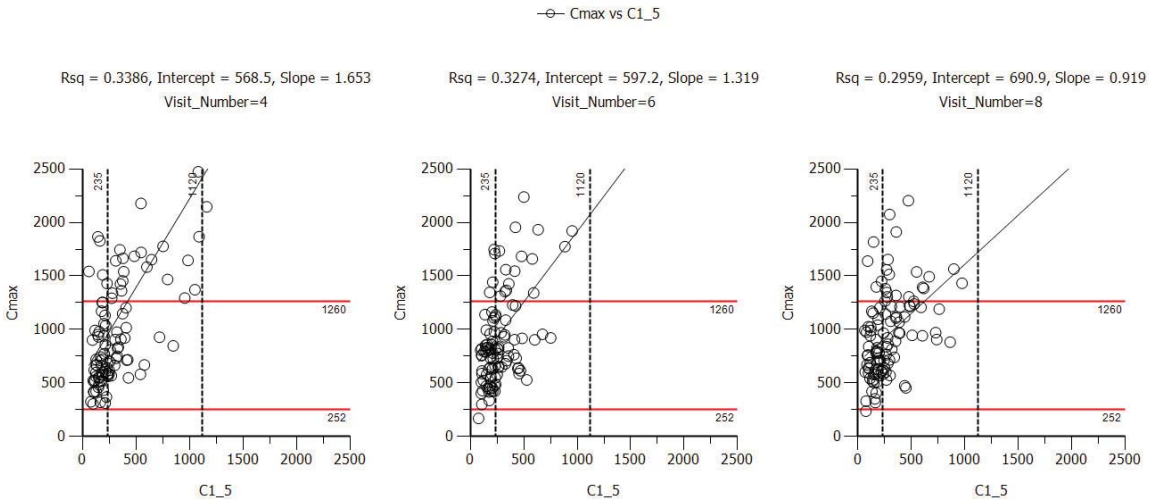
A correlation was explored using scatterplots and linear regression (with regression coefficient) on C_{max} vs. each timepoint of C_x on Phase III MRS-TU2019 study data (Figure 3). Table 19 summarizing regression coefficient indicates that there is a strong correlation (0.7~0.9) between C_{max} and C_x from 3-5 h for Visit 4 and 6, and a moderate correlation (~0.5) between C_{max} and C_x for 6 h for Visit 4 and 6; while a poor correlation (<0.5) between C_{max} and C_x for 0, 1.5, 8 and 12 h for Visit 4 and 6. These correlation analysis suggested that 3-6 h postdose (but not 0, 1.5, 8 and 12 h) may be suitable as the single blood draw window for making titration decisions.

Figure 3 Scatterplots of C_{max} vs. C_x on Phase III MRS-TU-2019 study data

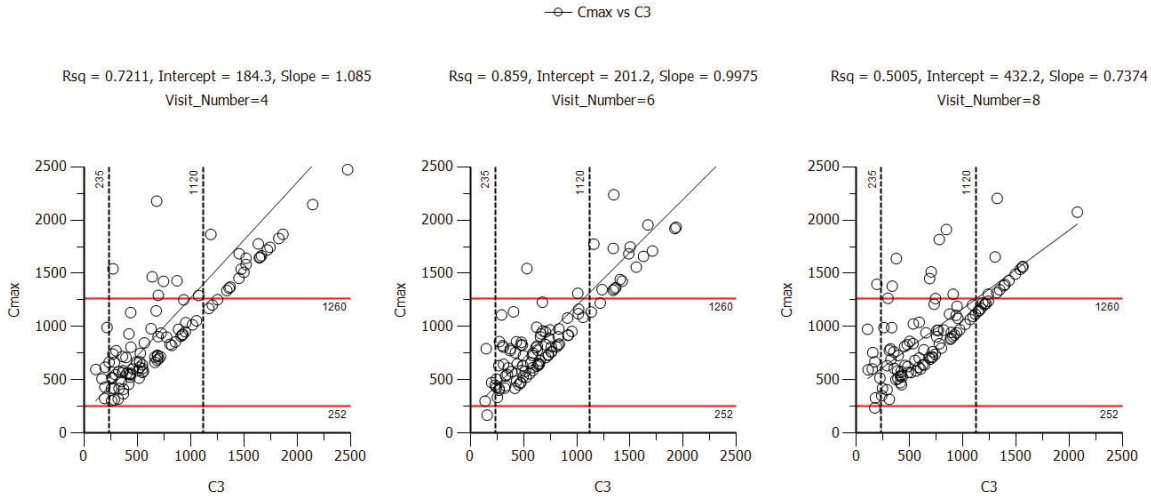
C_{max} vs. C_0



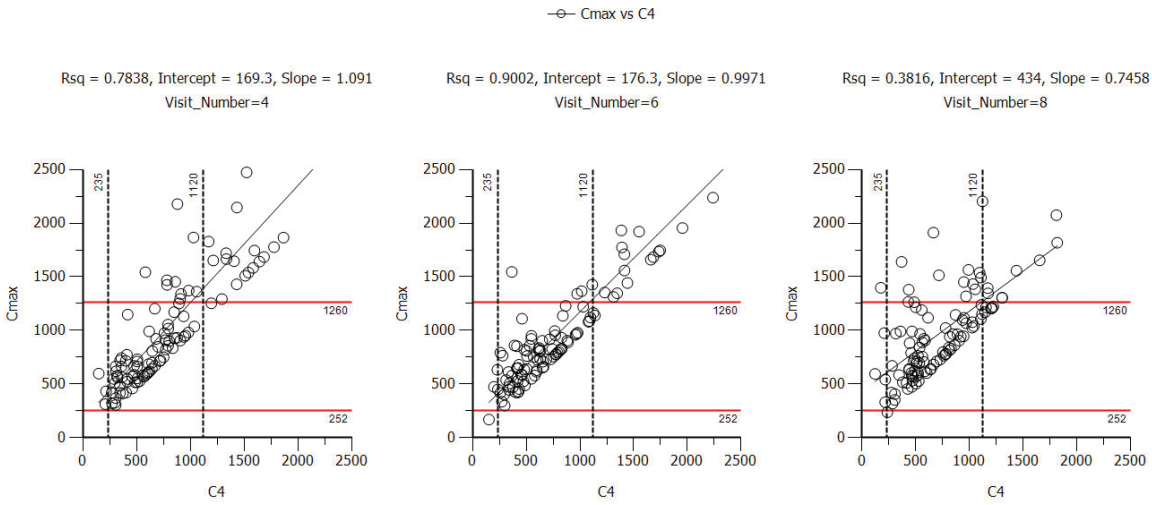
C_{max} vs. $C_{1.5}$



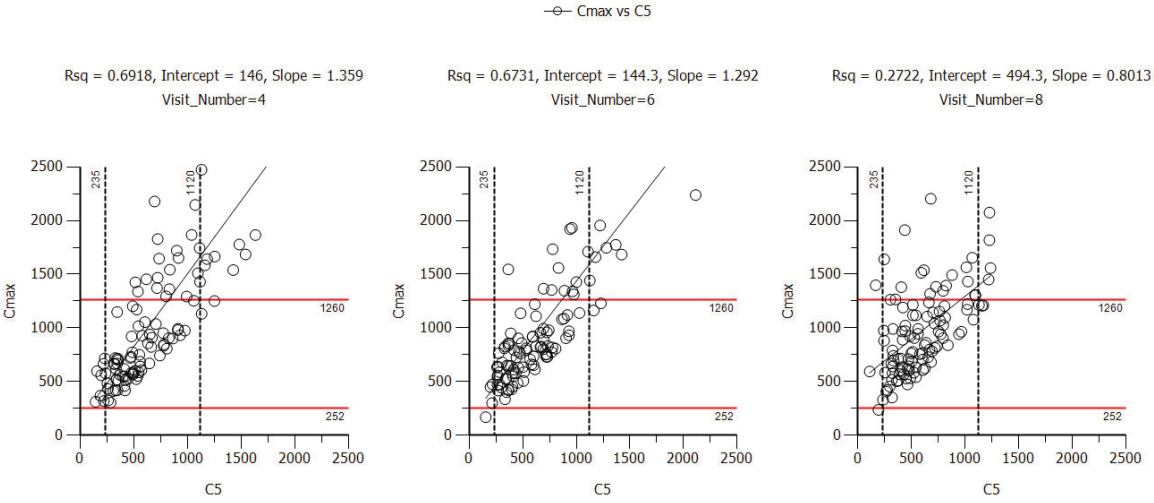
Cmax vs. C3



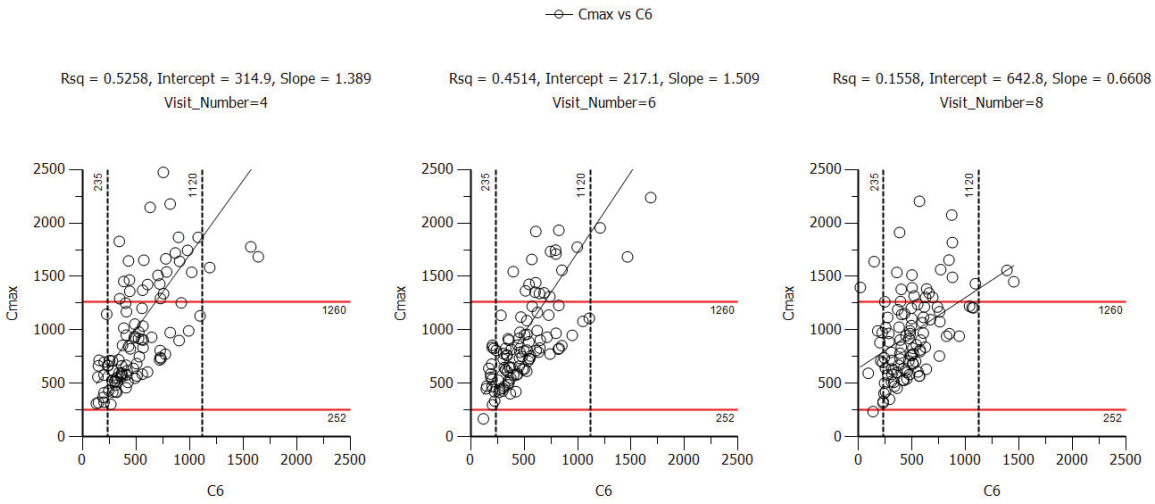
Cmax vs. C4



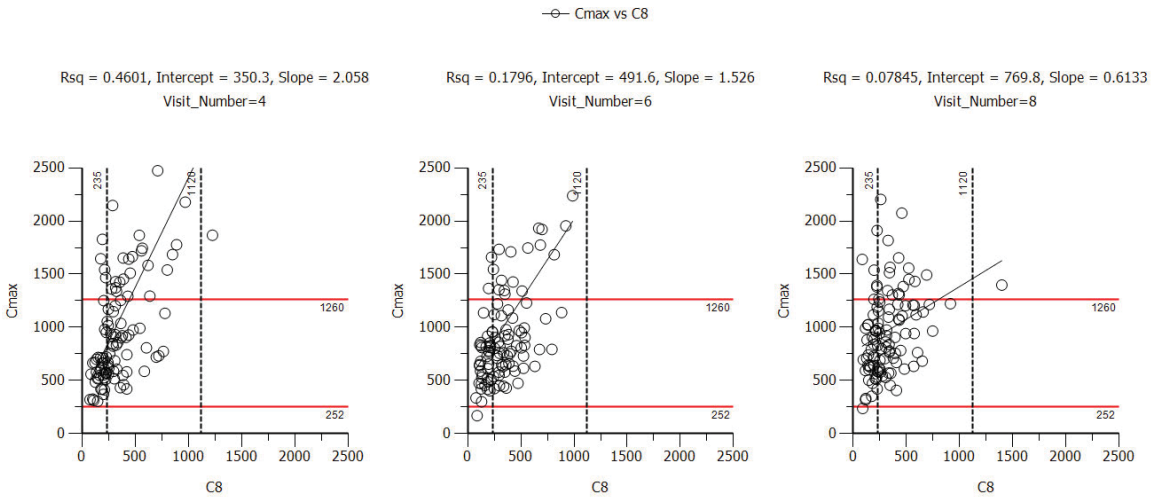
Cmax vs. C5



Cmax vs. C6



Cmax vs. C8



Cmax vs. C12

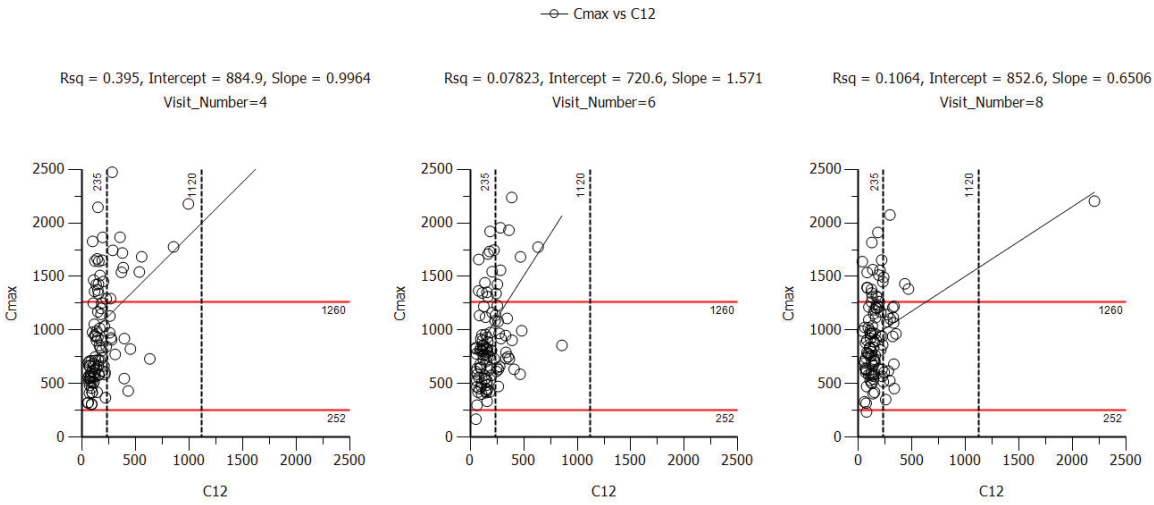


Table 17 Regression coefficient (R) for C_{max} vs. C_x.

C_x	Correlation (R) at Visit 4	Correlation (R) at Visit 6
0h	0.18	0.07
1.5h	0.34	0.33
3h	**0.72**	**0.86**
4h	**0.78**	**0.90**
5h	**0.69**	**0.67**
6h	0.53	0.45
8h	0.46	0.18
12h	0.40	0.08

Concordance analysis on simulated data 3-6 hours postdose window

Concordance analysis results are shown in Table 20 for C3, C4, C5, and C6 at visit 4 or visit 6 respectively. The total concordance at visit 4 were approximately 82, 92 and 90% for C3, C4, and C5 respectively, while 73% for C6. At visit 6, total concordance was only about 51% for C6 while those for C3, C4, C5 were at 71-83%. These results confirm that the 3-5 h window is optimum.

Cell definitions are given below the table. Note that Cells I and VI are omitted from the table, as there are no subjects in these categories. Numeric concordance records the percent of titration decisions based on C_x which are the same as if the decision was based on C_{avg}. Effective concordance records the percent of titration decisions where the titration based on C_x is incorrect with respect to C_{avg}, but the resulting C_{avg} remains within the normal range.

Table 20 Concordance Analysis (C_{avg} vs C_x) for MRS-TU-2019 for Time Post-Dose.

Time of T-Concentration	Numeric Concordance (NC)	Effective Concordance (EC)				Total Concordance (NC+EC)
	Cells A+B+C	Cell II	Cell III	Cell IV	Cell V	
Visit 4 (T-measurement for first dose titration opportunity)						
C3h	67.4	0	9.4	3.6	1.4	81.9
C4h	76.1	0	13.0	0.7	2.2	92.0
C5h	76.1	0	13.0	0	0.7	89.9
C6h	62.3	0	10.9	0	0	***73.2***
Visit 6 (T-measurement for second dose titration opportunity)						
C3h	61.6	0	7.2	1.4	0.7	***71.0***
C4h	70.3	0	10.9	0.7	1.4	83.3
C5h	63.0	0	10.9	0.7	0.7	***75.3***
C6h	44.9	0	6.5	0	0	***51.4***

The cells used for the concordance calculation as defined as:

Cell A: T-concentration < up-titration threshold and Cavg < lower limit of normal range.

Cell B: T-concentration between titration thresholds and Cavg within normal range.

Cell C: T-concentration > down-titration threshold and Cavg > upper limit of normal range.

Cell I: T-concentration < up-titration threshold and Cavg > upper limit of normal range. ***No subjects are found in this category and the cell is not included in concordance results.***

Cell II: T-concentration between titration thresholds and Cavg > upper limit of normal range

Cell III: T-concentration < up-titration threshold and Cavg within normal range

Cell IV: T-concentration between titration thresholds and Cavg < lower limit of normal range

Cell V: T-concentration > down-titration threshold and Cavg within normal range

Cell VI: T-concentration > down-titration threshold and Cavg < lower limit of normal range. ***No subjects are found in this category and the cell is not included in concordance results.***

Conclusions:

Modeling and simulations based on Phase III MRS-TU2019 study data demonstrates that the 400-900 ng/dL up- and down-titration cutoffs are appropriate for 200mg a.m./200mg a.m. starting dose. Concordance analysis on simulated data identifies 3-5 h postdose as the appropriate window for single blood draw to make titration decisions. These titration thresholds and starting dose are used in MRS-TU-2019EXT.

16.3. HANDLING OF DATA FOR DUPLICATE SUBJECTS

Three subjects were randomized into the MRS-TU-2019 study twice in error. Each subject and randomization were assigned a unique subject identifier. As such, these 3 subjects are represented within MRS-TU-2019 datasets as six subject identifiers. The circumstances with respect to each of these subjects are different hence for population assignment and analysis purposes, they are addressed separately.

- Subject 'A': Subject Identifier 107157 and Subject Identifier 139969

Subject 'A' was first randomized to SOV2012-f1. He participated through Day 90 as 107157 before randomizing a second time and receiving study drug (Androgel) as 139969. He then received Androgel and SOV simultaneously while completing the study on SOV2012-f1. Since Androgel was a coadministration, only 107157 is being summarized and analyzed. The one modification to this is that any AEs that occur under either subject identifier will be attributed to 107157.

Subject 'A' did not participate in MRS-TU-2019EXT under either subject identifier:

Population	107157	139969
Safety Set	Include	Exclude
Full Analysis Set	Include	Exclude
Pharmacokinetic Set	Include	Exclude
Efficacy Completers Set	Include	Exclude
Extension Treated Set	n/a	n/a
Overall Safety Set	Include	Include under 107157

- Subject 'B': Subject Identifier 107270 and Subject Identifier 1391208

Under the first randomization (SOV2012-f1 under Subject Identifier 107270), subject 'B' received no study drug as he enrolled and early termed the same day. He enrolled at a different site about four months later and completed MRS-TU-2019 as Subject Identifier 1391208. As Subject 'B' was not dosed under Subject Identifier 107270, he was deemed ineligible for any study populations under this identifier. But Subject 'B' was included in most analysis sets under Subject Identifier 1381208. Subject identifier 1381208 also participated in MRS-TU-2018EXT:

Population	107270	1391208
Safety Set	n/a	Include
Full Analysis Set	n/a	Include
Pharmacokinetic Set	n/a	Include

Efficacy Completers Set	n/a	Include
Extension Treated Set	n/a	Include
Overall Safety Set	n/a	Include

- Subject 'C': Subject identifier 107274 and Subject identifier 1391174

Under the first randomization (SOV2012-f1 under Subject Identifier 107274), Subject 'C' received study drug but was lost to follow-up prior to any post baseline assessments. He enrolled at a different site about four months later and completed MRS-TU-2019 as Subject Identifier 1391174. As Subject 'C' was given study treatment under Subject Identifier 107274, he was deemed eligible for some study populations under this identifier. Subject 'C' was also included in most analysis sets under Subject Identifier 1381174. Subject identifier 1381174 also participated in MRS-TU-2018EXT:

Population	**107274**	**1391174**
Safety Set	Include	Include
Full Analysis Set	Include*	Include
Pharmacokinetic Set	Exclude	Include
Efficacy Completers Set	Exclude	Include
Extension Treated Set	n/a	Include
Overall Safety Set	Exclude**	Include

*Because Subject Identifier 107274 did not have any post baseline pk profiles, it will be treated as an efficacy failure.
**This exclusion is considered a conservative approach as Subject Identifier 107274 did not report any AEs.

Subject 'C' will be the only dual randomized subject with two subject identifiers being summarized in tables and figures in MRS-TU-2019.

All data from these six subject identifiers will be listed.

16.4. OUTLIER ANALYSIS FOR SITE 104

16.4.1. Objective

The objective of this analysis is to develop an algorithm to identify outlier profiles that may indicate a process deviation.

Marius obtained at Day 90E 24-hr serum PK samples (for the MRS-TU-2019EXT Serum Substudy) in addition to the 24-hr NaF/EDTA plasma PK samples. Upon inspection of the data, the ratio of the NaF/EDTA plasma to serum values seemed anomalous . Marius has previously examined these ratios,

such as in the Phase 2b study SOV-TU-PK2013 to understand the implications of using serum samples for TRT titration with SOV2012-F1.

Laboratory and clinical data (e.g. SOV-TU-PK2013) have long shown that in properly acquired and handled samples, the serum value will generally equal or exceed the NaF/EDTA plasma value, especially at timepoints drawn during peak T or peak TU concentrations. For Site 104, this ratio was consistently inverted over much (or all) of the PK timepoints for a substantial number of subjects. These sets of observations prompted the outlier analysis.

16.4.2. Study Population

16.4.3. Sample Size

Data is provided by 103 subjects.

16.4.4. Data Analysis and Report

Analysis Population

This analysis utilizes all subjects with serum and plasma NaF/EDTA results from the serum substudy.

Statistical Analysis Methods

All serum and plasma results are natural log transformed prior to analysis.

Within each subject and visit, the difference between plasma and serum is taken: Diff=plasma-serum. The distribution of this difference in natural log values is characterized by producing mean, median, and standard deviations.

Each of these differences is evaluated for an outlier status by determining if it is outside the upper range as defined by 1.96*std which is in the upper 2.5 %. Only the upper range is used since the expectation (the 'null' hypothesis) is that the serum would be greater than or equal to the plasma.

H_0: plasma <=serum.

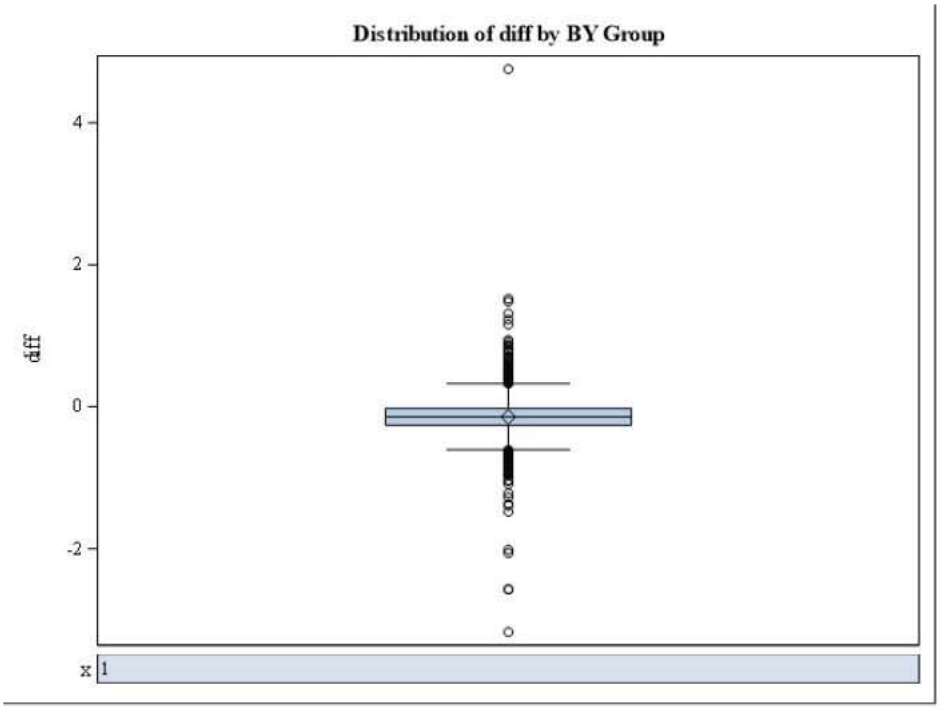
Ha: plasma >serum

Next, then the number of individual outliers is counted within a profile to determine if a profile is in of itself an outlier.

If the number of outliers within a profile (15 assessments within a profile) is required to be 4 or more, the outlier probability as determined by the hypergeometric distribution is 0.0003. If the number of outliers within a profile (15 assessments within a profile) is required to be 3 or more, the outlier probability as determined by the hypergeometric distribution is 0.005.

16.4.5. Results

One hundred and three subjects were assessed for serum and plasma testosterone. A total of 3488 timepoints across subjects had both serum and plasma results. As such the distribution was defined by a large number of subjects. A boxplot of the differences in log transformed data follows:



Summary statistics includes the following:

Basic Statistical Measures			
Location		**Variability**	
Mean	-0.14315	**Std Deviation**	0.25035
Median	-0.14232	**Variance**	0.06267
Mode	.	**Range**	7.93419
		Interquartile Range	0.23586

Using this mean and standard deviation the following subjects had outliers at least once in their Visit 26 profile:

Subject	Frequency	Percent	Cumulative Frequency	Cumulative Percent
101773	1	1.89	1	1.89
104132	2	3.77	3	5.66
104197	6	11.32	9	16.98
104388	3	5.66	12	22.64
104407	8	15.09	20	37.74
104754	6	11.32	26	49.06
104793	2	3.77	28	52.83
107668	3	5.66	31	58.49
107807	1	1.89	32	60.38
111878	1	1.89	33	62.26
123674	1	1.89	34	64.15
133514	1	1.89	35	66.04
1041226	2	3.77	37	69.81
1041568	4	7.55	41	77.36
1041613	7	13.21	48	90.57
1111581	2	3.77	50	94.34
1131802	1	1.89	51	96.23
1201246	1	1.89	52	98.11
1201359	1	1.89	53	100.00

Integrating the requirement for at least 3 outliers, the list is narrowed to the following:

Obs	Visit	Subject	COUNT	PERCENT
2	26	104197	6	11.3208
3	26	104388	3	5.6604
4	26	104407	8	15.0943
5	26	104754	6	11.3208
6	26	107668	3	5.6604
7	26	1041568	4	7.5472
8	26	1041613	7	13.2075

Integrating the requirement for at least 4 outliers, the list is further reduced as follows:

Obs	Visit	Subject	COUNT	PERCENT
1	26	104197	6	11.3208
2	26	104407	8	15.0943
3	26	104754	6	11.3208
4	26	1041568	4	7.5472