Statistical Analysis Plan for Study M19-161

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

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Version 2.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for Androgel 1.62% Study M19-161 24-Hour Ambulatory Blood Pressure Monitoring Study in Hypogonadal Men Receiving Testosterone Replacement Therapy.

Study M19-161 assesses the effect of Androgel 1.62% on blood pressure (BP) in hypogonadal men.

The analyses of pharmacokinetic endpoints will not be covered in this SAP.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later under the UNIX operating system.

2.0 Study Design and Objectives

2.1 Objectives and Hypotheses

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

2.2 Study Design Overview

This is a multicenter, Phase 4, open-label, single-arm study to establish that the average 24-Hour SBP at End of Treatment (EOT) is not greater than Baseline SBP with a non-inferiority margin of 3 mmHg. Efficacy will not be evaluated in this study.

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

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

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

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

The validity of the ABPM 24-hour collection measurements will be evaluated prior to performing the procedures for the Day 1 Visit, and prior to performing the procedures for the EOT Visit. Day 1 is defined as start of treatment (first dose of the study drug). Subjects will receive the first dose of the study drug on site only after validity of the baseline ABPM 24-hour collection is confirmed.

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

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

an ABPM device malfunction. Based on these criteria, a 24-hour ABPM collection will be considered valid if all of the following are obtained:

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

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

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

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

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

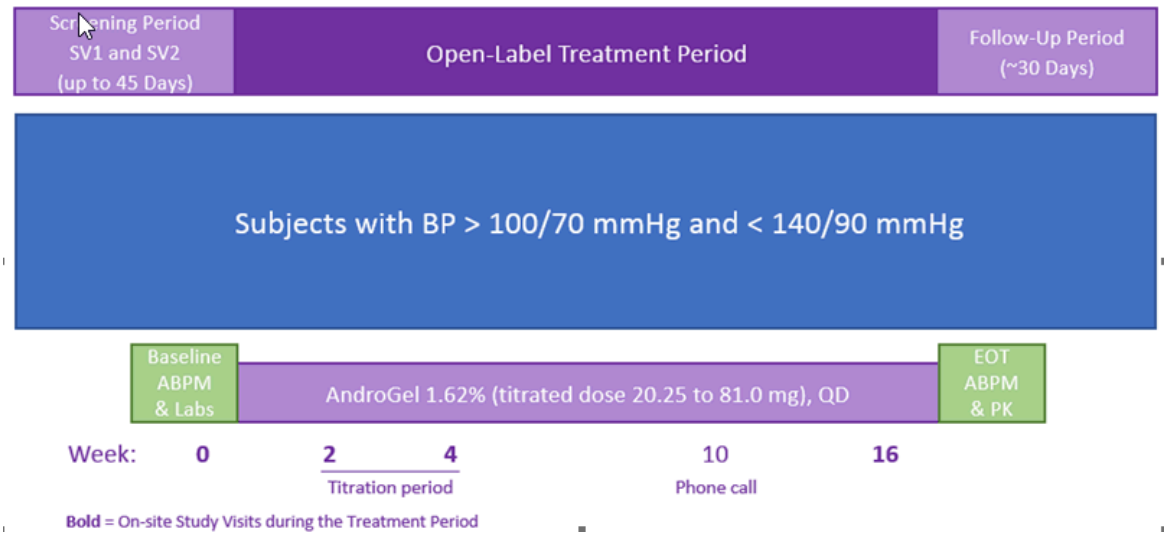
A Follow-up Visit phone call will occur approximately 30 days after the last dose of study drug. During phone calls and in-person visits throughout the study, subjects will be asked specific questions pertaining to the possible occurrence of SAEs, adverse events of special interest (AESI), adverse events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

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

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

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



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

2.3 Treatment Assignment and Blinding

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

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

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

2.4 Sample Size Determination

A sample size of 171 subjects will provide 90% power for a paired t-test with 0.025 one-sided significance level to show that the EOT average 24-hour SBP is not greater than the Baseline average 24-hour SBP with a non-inferiority margin of 3 mmHg, assuming the mean difference between EOT and Baseline is an increase of 0.5 mmHg and the SD of the difference is 10 mmHg. The power for the primary analysis using linear regression with covariate adjustment for baseline will be as least as high as that from the paired t-test. Assuming a 10% loss of subjects from the per protocol population due to premature discontinuation, invalid ABPM at the Baseline or EOT visit, or non-adherence to study drug, approximately 190 subjects will be enrolled to reach a minimum of 171 subjects who are at least 85% compliant to study drug and have valid ABPM data from Baseline and the EOT visits.

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

3.0 Endpoints

3.1 Primary Endpoint

The primary endpoint is the mean change in 24-hour average SBP from Baseline to EOT.

3.2 Other Endpoints

- Change from Baseline to EOT in average daytime (09:00 – 21:00 h) mean arterial pressure (MAP), SBP, diastolic blood pressure (DBP), pulse pressure (PP), and heart rate (HR)
- Change from Baseline to EOT in average nighttime (01:00 – 06:00 h) MAP, SBP, DBP, PP, and HR
- Change from Baseline to EOT in average 24-hour MAP, DBP, PP, and HR

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

3.3 Safety Endpoint(s)

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

3.4 Additional Endpoint(s)

The analyses of pharmacokinetic endpoints will not be covered in this SAP.

4.0 Analysis Populations

The following population sets will be used for the analyses.

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

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

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

5.0 Subject Disposition

A summary of subject accountability will be provided where the number of subjects in each of the following categories will be summarized for all enrolled subjects:

- Subjects enrolled in the study.
- Subjects who took at least one dose of study drug.
- Subjects who completed protocol-specified treatment.
- Subjects who completed study.
- Subjects who prematurely discontinued study drug (all reasons and primary reason).
- Subjects who prematurely discontinued study (all reasons and primary reason).
- Subjects in each analysis population, as applicable.

6.0 Study Drug Duration and Compliance

For the FAS and per protocol population, duration of treatment will be summarized. Duration of treatment is defined for each subject as last dose date minus first dose date + 1. Duration of treatment will be summarized using the number of subjects treated,

mean, standard deviation, median, minimum and maximum. In addition, the number and percentage of subjects in each treatment duration interval (0 to < 16 weeks, and ≥ 16 weeks) will be summarized.

Compliance

Treatment compliance will be summarized for the entire treatment period for the FAS and per protocol population, separately. Treatment compliance is defined as the weight of the drug actually utilized divided by the weight of the drug that should have been utilized. Percent compliance will be summarized.

Step 1: Calculate the number of days between visits and possible titration dates

To calculate compliance for each subject, let D_0, D_1, D_2, D_3, D_4, D_5 and D_6 be defined as:

$$D_0 = \begin{cases} number\ of\ days\ between\ Day\ 1\ visit\ and\ Week\ 2\ visit \\ \quad Week\ 2\ visit\ date - Day\ 1\ visit\ date + 1 \end{cases}$$

$$D_1 = \begin{cases} number\ of\ days\ between\ Week\ 2\ visit\ and\ Week\ 2\ Titration \\ \quad Week\ 2\ Titration\ date - Week\ 2\ visit\ date + 1 \end{cases}$$

$$D_2 = \begin{cases} number\ of\ days\ between\ Week\ 2\ Titration\ and\ Week\ 4\ visit \\ \quad Week\ 4\ visit\ date - Week\ 2\ Titration\ date + 1 \end{cases}$$

$$D_3 = \begin{cases} number\ of\ days\ between\ Week\ 4\ visit\ and\ Week\ 4\ Titration \\ \quad Week\ 4\ Titration\ date - Week\ 4\ visit\ date + 1 \end{cases}$$

$$D_4 = \begin{cases} number\ of\ days\ between\ Week\ 4\ Titration\ and\ EOT\ visit \\ \quad EOT\ visit\ date - Week\ 4\ Titration\ date + 1 \end{cases}$$

If there is no titration between Week 2 and Week 4 visits, then

$$D_5 = \begin{cases} number\ of\ days\ between\ Week\ 2\ visit\ and\ Week\ 4\ visit \\ \quad Week\ 4\ visit\ date - Week\ 2\ visit\ date + 1 \end{cases}$$

If there is no titration between Week 4 and EOT visits, then

$$D_6 = \begin{cases} number\ of\ days\ between\ Week\ 4\ visit\ and\ EOT\ visit \\ \quad EOT\ visit\ date - Week\ 4\ visit\ date + 1 \end{cases}$$

Step 2: Calculate weight of the prescribed dose (A) and P_{avg}

Let P_0, P_1, P_2, P_3 and P_4 be the study drug actuations assigned at the Day 1 visit date, Week 2 visit date, Week 2 Titration date, Week 4 visit date, and Week 4 Titration date, respectively.

a. Case 1: there is titration after Week 2 visit and after Week 4 visit

The weight of the prescribed actuations (A) is defined by:

$$A = \left((D_0 * P_0 + D_1 * P_1 + D_2 * P_2 + D_3 * P_3 + D_4 * P_4) * 1.25\right) \text{mg}$$

The average actuations, P_{avg}, over the treatment period is defined as:

$$P_{avg} = \frac{D_0 * P_0 + D_1 * P_1 + D_2 * P_2 + D_3 * P_3 + D_4 * P_4}{D_0 + D_1 + D_2 + D_3 + D_4}$$

b. Case 2: there is titration after Week 2 visit but NOT after Week 4 visit

A is defined by:

$$A = ((D_0 * P_0 + D_1 * P_1 + D_2 * P_2 + D_6 * P_3) * 1.25) \text{ mg}$$

The average actuations, P_{avg}, over the treatment period drug duration is defined as:

$$P_{avg} = \frac{D_0 * P_0 + D_1 * P_1 + D_2 * P_2 + D_6 * P_3}{D_0 + D_1 + D_2 + D_6}$$

c. Case 3: there is titration after Week 4 visit but NOT after Week 2 visit

A is defined by:

$$A = ((D_0 * P_0 + D_5 * P_1 + D_3 * P_3 + D_4 * P_4) * 1.25) \text{ mg}$$

The average actuations, P_{avg}, over the treatment period is defined as:

$$P_{avg} = \frac{D_0 * P_0 + D_5 * P_1 + D_3 * P_3 + D_4 * P_4}{D_0 + D_5 + D_3 + D_4}$$

d. Case 4: there is NO titration after Week 2 visit nor after Week 4 visit

A is defined by:

$$A = ((D_0 * P_0 + D_5 * P_1 + D_6 * P_3) * 1.25) \text{ mg}$$

The average actuations, P_{avg}, over the treatment period is defined as:

$$P_{avg} = \frac{D_0 * P_0 + D_5 * P_1 + D_6 * P_3}{D_0 + D_5 + D_6}$$

Step 3: Calculate weight of the utilized study drug (*B*)

Define the following:

n_0: number of bottles utilized and returned

n_1: number of missing bottles completely used (never returned)

n_2: number of missing bottles partially used (never returned)

x: number of days the partially used missing bottles are used in total

W_0: total weight of the n_0 bottles that were utilized and returned

B_1: the weight of the study drug utilized in returned bottles

B_2: the weight of the drug utilized after adjusting for the missing bottles completely used

B: the weight of all study drug utilized by the subject (adjusting for missing bottles completely or partially used)

The weight of the study drug utilized from returned bottles = $B_1 = n_0 * 131 - W_0$.

If $n_1 = 0$, $B_2 = B_1$; *if* $n_1 > 0$, $B_2 = B_1 + (n_1 * 75)$ assuming 75 mg used in every completely used never returned bottle.

If $n_2 = 0$, $B = B_2$; if $n_2 > 0$, $B = B_2 + ((n_2 * P_{avg}) * 1.25)$ assuming that the average number of actuations used in the rest of the bottles was used in each partially used and never returned bottle.

Step 4: Calculate compliance over the treatment period

Compliance percentage (C) over the treatment period is defined as:

$$C = \frac{B}{A} * 100$$

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics and baseline characteristics will be summarized for the FAS and per protocol population. Medical history and prior and concomitant medications will be summarized for the FAS only. Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum).

7.1 Demographics and Baseline Characteristics

Continuous demographic variables include age, weight, height, body mass index (BMI), and arm circumference. Categorical demographic variables include ethnicity [Hispanic/Latino, Not Hispanic/Latino], race, age (18 years – < 45 years, 45 years – < 65 years, ≥ 65 years), BMI (< 25 or ≥ 25 kg/m^2), tobacco user (current, former, never, unknown), and alcohol user (current, former, never, unknown).

Continuous baseline characteristics include testosterone value, PSA, hematocrit, office SBP, office DBP, heart rate (HR), respiratory rate (RR), oral body temperature, creatinine, hemoglobin A1c. Categorical baseline characteristics include ongoing medical history of

hypertension (Yes/No), diabetes status at Baseline (Yes/No), anti-hypertensive medication at Baseline (Yes/No), ongoing medical history with anti-hypertensive medication at Baseline (medical history of hypertension with medication, medical history of hypertension without medication, no medical history of hypertension without medication), ECG (normal/abnormal), DRE (normal/abnormal), PSA (≤ 3 ng/mL and > 3 ng/mL) and hemoglobin A1c (< 6.5% and ≥ 6.5%).

7.2 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class and preferred term) will be summarized. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term). No statistical comparison will be performed on medical history.

7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized separately by generic name. Hypertensive medications, both prior and concomitant medications, will be summarized separately by generic name.

A prior medication is defined as any medication taken prior to the first dose of study drug. This includes medications with a start date before the first study drug administration date, regardless of the end date of these medications. In cases where incomplete or missing medication dates are collected, a conservative approach will be taken such that if a medication could have been a prior medication, it will be counted as a prior medication.

A concomitant medication is defined as any medication, other than the study drug, that started prior to the date of the first dose of study drug and continued to be taken after the first dose of study drug or any medication that started on or after the date of the first dose

of study drug, but not after the date of the last dose of study drug. In the situation where an incomplete or missing medication date is collected, a conservative approach will be taken such that if a medication could have been a concomitant medication, it will be counted as a concomitant medication. A medication will be considered a concomitant medication where one of the following three cases occurs (1) the start date is missing and the end date is either after or on the first study drug dose date; (2) the start date is prior to or on the last dose of study drug and the end date is missing; (3) both the start date and the end date are missing.

Note that a medication can be considered both a prior and concomitant medication if it started prior to the first dose of study drug and continued after the first dose of study drug.

The number and percentage of subjects in the FAS population taking medications will be summarized by generic drug name based on the World Health Organization (WHO) Drug Dictionary for both prior and concomitant medications.

Prior and concomitant medications for hypertension will be summarized separately.

8.0 Efficacy Analyses

Efficacy will not be evaluated in this study.

9.0 Safety Analyses

9.1.1 Primary Safety Endpoint

The primary endpoint is the change in 24-hour average SBP from Baseline to EOT.

9.1.2 Handling of Missing Data for the Primary Safety Endpoint

The ABPM data will be collected for 24 hours both at Baseline and EOT. The ABPM data will be considered valid if at least 50% measurements are recorded during the 24-hour period, daytime period (09:00 – 21:00), and nighttime period (01:00 – 06:00), i.e., at least 24 measurements of SBP during the 24-hour period, at least 12 SBP

measurements between 9:00 to 21:00, and at least 5 measurements between 1:00 and 6:00. If the above criteria are not met, the ABPM collection will not be considered as valid.

For the primary analysis of the primary safety endpoint, subjects in the per protocol population will have both valid Baseline ABPM collection as well as valid EOT ABPM collection. For the primary analysis, average 24-hour SBP will be used and no missing data imputation will be performed for the missing ABPM measurements within a valid ABPM collection.

Sensitivity analyses 1 and 2 using all individual ABPM measurements using multiple imputation will be performed on subjects in the FAS population who are at least 85% compliant to the study drug and in the per protocol population, respectively. Missing ABPM measurements within the 24-hour duration at both Baseline and EOT will be imputed with multiple imputation. Missing data mechanism of Missing at Random (MAR) is assumed in these analyses.

Sensitivity analysis 3 will be performed on subjects in the FAS population who are at least 85% compliant to the study drug. A mixed model with repeated measures analysis using average 24-hour SBP (including both valid EOT and Baseline collections) as the outcome variable will be performed. In this analysis, no missing data imputation will be performed for the missing ABPM measurements within a valid ABPM collection.

A supportive analysis examining effect of day of the week will be performed on subjects in the per protocol population. Average 24-hour SBP will be used and no missing data imputation will be performed for the missing ABPM measurements within a valid ABPM collection.

9.1.3 Primary Safety Analysis

The hypothesis for the primary safety analysis is,

H_0: Change in 24-hour average SBP from Baseline to EOT $\geq$ 3 mmHg

Vs. H_1: Change in 24-hour average SBP from Baseline to EOT < 3 mmHg

The primary endpoint of change from Baseline to EOT in average 24-hour SBP will be evaluated using a linear regression model with change in average 24-hour SBP from Baseline to EOT as the dependent variable, centralized baseline average 24-hour SBP, ongoing medical history of hypertension, and pooled study center as covariates in the per protocol population.

Denote:

y = change from Baseline to EOT in average 24-hour SBP

x = average 24-hour SBP at Baseline

μ_x = mean of the average 24-hour SBP at Baseline

C = pooled study center indicator, c = 1, 2, ..., m

μ_c = coefficient of pooled study center indicator for pooled study center c

H = stratum of ongoing medical history of hypertension indicator, h = Y, N

μ_h = coefficient of ongoing medical history of hypertension indicator for stratum h

N = total sample size

Nc = sample size for center c

N_h = sample size for stratum h

α = intercept

β = coefficient of the centralized Baseline average 24-hour SBP

ε = error term

The model could be represented as,

$$y = \alpha + \beta(x - \mu_x) + \sum_{c=1}^{m} \mu_c \, I(C = c) + \sum_{h=1}^{2} \mu_h \, I(H = h) + \varepsilon$$

The primary endpoint will be evaluated by least squares estimate and 1-sided 97.5% confidence interval (CI) of mean change in the average 24-hour SBP from Baseline to EOT (i.e., $\alpha + \sum_{c=1}^{m}(N_c/N)\mu_c + \sum_{h=1}^{2}(N_h/N)\mu_h$). If the upper confidence limit of the 1-sided CI is less than 3 mmHg, this will establish that the baseline average 24-hour SBP at EOT is not greater than Baseline with a non-inferiority margin of 3 mmHg.

Pooled Study Center

To define pooled study centers, the study sites will first be pooled by geographic locations. Table 1 displays the states that are included in the four regions of the United States according to the Unites States Census Bureau.[1]

Table 1. Regions of the United States

Region 1: Northeast	Region 2: Midwest	Region 3: South	Region 4: West
Connecticut	Indiana	Delaware	Arizona
Maine	Illinois	District of Columbia	Colorado
Massachusetts	Michigan	Florida	Idaho
New Hampshire	Ohio	Georgia	New Mexico
Rhode Island	Wisconsin	Maryland	Montana
Vermont	Iowa	North Carolina	Utah
New Jersey	Kansas	South Carolina	Nevada
New York	Minnesota	Virginia	Wyoming
Pennsylvania	Missouri	West Virginia	Alaska
	Nebraska	Alabama	California
	North Dakota	Kentucky	Hawaii
	South Dakota	Mississippi	Oregon
		Tennessee	Washington
		Arkansas	
		Louisiana	
		Oklahama	
		Texas	

If a pooled geographic region has more than 25% of the study subjects, then the sites in this pooled study center will be randomly separated into two pooled centers in that region.

9.1.3.1 Sensitivity Analyses of the Primary Safety Endpoint

Sensitivity Analysis 1

This sensitivity analysis will use all ABPM observations on subjects in FAS population who are at least 85% compliant to study drug.

1. Missing ABPM measurements (timepoints 1, 2, 3, ..., 47, 48) at both Baseline and EOT will be imputed by multiple imputation in the following 3 steps. **Multiple Imputation:** (a) *30* "complete" datasets of ABPM measurements (48 timepoints) at Baseline will be generated via MCMC IMPUTE = FULL option using SAS PROC MI.[2] The strata of ongoing medical history of hypertension and pooled

study center will be included in the imputation model as covariates. Random seed 12345 will be used; (b) For each subject, Baseline ABPM measurements will be calculated by taking the average over *30* "complete" datasets obtained in (a); (c) *30* "complete" datasets of ABPM measurements (48 timepoints) at EOT will be generated via MCMC IMPUTE = FULL option using PROC MI[2] in SAS. The imputation model will include Baseline ABPM measurements obtained in (b), ongoing medical history of hypertension, and pooled study center as covariates. Random seed 34567 will be used.

2. **Analysis:** each of the *30* imputed datasets will be analyzed separately using the same linear regression model as in the primary safety analysis.
3. **Pooling:** estimates from step 2 will be combined into one overall pooled estimate using PROC MIANALYZE[3] in SAS.

Sensitivity Analysis 2

This sensitivity analysis will repeat the analysis using multiple imputation as described in Sensitivity Analysis 1 in the per protocol population.

Sensitivity Analysis 3

This sensitivity analysis will be performed on subjects in FAS population who are at least 85% compliant to study drug.

A repeated measures analysis model will be used with the 24-hr average SBP (including both valid EOT and Baseline collections) as outcome variable, fixed effects of visit (EOT, Baseline), fixed covariates of strata of ongoing medical history of hypertension and pooled study center, and the interaction effects of visit*strata and visit*center. The REPEATED statement will be used for visit in PROC MIXED. An unstructured covariance structure will be used. If the model fails to converge, a simplified covariance structure will be explored.

9.1.3.2 Supportive Analyses of the Primary Safety Endpoint

1. **Analysis examining effect of collection day of the week**

   An analysis will be conducted on the per protocol population to assess the effect of conducting the ABPM collection on weekdays vs. on weekends. If the ABPM collection started on Saturdays or Sundays, it is considered as a weekend collection, otherwise, it is considered as a weekday collection.

   A repeated measures analysis model will be used with the 24-hr average SBP (including both valid EOT and Baseline collections) as outcome variable, fixed effects of visit (EOT, Baseline), day effect (Weekend, Weekday), the interaction effect (visit * day effect), and fixed covariates of strata of ongoing medical history of hypertension and pooled study center. Test for the interaction effect will be conducted to see if the day of collection has any effect on the change from Baseline to EOT in ABPM data.

2. **Association between Data Missingness and Baseline Variables.**

   A stepwise logistic regression analysis will be conducted in the FAS to assess the association between the data missingness and key baseline clinical and demographic variables. The dependent variable will be whether the subject had valid ABPM data of SBP or not at EOT. Continuous independent variables will include baseline age, BMI, testosterone value, PSA, hematocrit, creatinine, hemoglobin A1c, average 24-hour SBP, and average 24-hour DBP. Categorical independent variables will include ethnicity, race, tobacco use, alcohol use, ongoing medical history of hypertension, anti-hypertensive medication at Baseline, and pooled study center. Additional variables may be added if deemed clinically meaningful.

9.2 Other Safety Endpoints and Analyses

9.2.1 Handling of Missing Data for Other Safety Endpoints

For the summary of other safety endpoints in Section 9.2.2, the average SBP, DBP, MAP, PP, and HR will be calculated separately for the 24-hour period, daytime, nighttime, and hourly using available data. The analyses will be performed on the per protocol population, except the BP outlier analysis. No missing data imputation will be performed for missing measurements within an ABPM collection.

9.2.2 Other Safety Endpoints

The continuous endpoints, for example, change from Baseline to EOT in average daytime, nighttime, 24-hour period, and measurement at T_{max} for DBP, SBP, MAP, PP and HR, will be summarized by mean, median, standard deviation, minimum and maximum.

The same linear regression model as in the primary analysis of the primary safety endpoint will be performed on the change from Baseline to EOT in average daytime SBP/DBP/MAP, nighttime SBP/DBP/MAP, and 24-hour DBP/MAP. The linear regression model will be evaluated with change from Baseline to EOT in the corresponding variable as the dependent variable, and corresponding centralized baseline value, strata of ongoing medical history of hypertension, and pooled study center as covariates in the per protocol population.

Change from Baseline to EOT for hourly average of MAP, SBP, DBP, PP and HR will also be summarized by mean, median, standard deviation, minimum and maximum by both nominal clock time and by time after dose.

The categorical endpoints (e.g., subjects with new concomitant anti-hypertensive medications and subjects with dose increase in anti-hypertensive medication during the treatment period) will be summarized with n and percentage.

Subjects meeting the following BP thresholds separately by 24-hour average and by hourly average by 24-hour recordings will also be summarized categorically.

- ≥ 160 mmHg SBP at EOT
- ≥ 100 mmHg DBP at EOT
- ≤ 90 mmHg SBP at EOT
- ≤ 60 mmHg DBP at EOT
- ≥ 20 mmHg increase from Baseline to EOT in SBP
- ≥ 15 mmHg increase from Baseline to EOT in DBP

Listings of subjects with the BP categories as above will also be provided. The BP outlier analysis as described above will be performed on the Safety analysis set.

The following additional analysis will be performed:

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

Summary of frequency of data completeness of ABPM measurement data of SBP (0,1 or 2) both at Baseline and EOT will be provided by hour over the 24-hour time frame.

9.3 Safety Subgroup Analyses

All the analyses for the primary (except supplementary and sensitivity analyses) and other safety endpoints will also be provided by the following subgroups:

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

The primary safety analysis will be performed at each subgroup level for the following subgroup variables:

- Race;
- Ongoing medical history of hypertension;
- Diabetes status.

10.0 Additional Safety Analyses

10.1 General Considerations

Additional safety data including adverse events, clinical laboratory data, and vital signs will be summarized for the Safety Analysis Set.

10.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

10.2.1 Treatment-emergent Adverse Event (TEAE)

Treatment-emergent AEs are defined as any AE with the onset that is after the first dose of study drug. AEs starting more than 30 days following discontinuation of study drug will not be included in summaries related to treatment-emergent AEs. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent.

10.2.2 Adverse Event Overview

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any treatment-emergent SAE
- Any treatment-emergent AE leading to discontinuation of study drug
- Any treatment-emergent AE leading to death
- Any treatment-emergent AE of hypertension
- All deaths

10.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

Treatment emergent AESI, AEs leading to study drug discontinuation and SAEs will be summarized in descending order of overall frequency by Medical Dictionary for Regulatory Activities (MedDRA) preferred term, as well as by system organ class (SOC) and MedDRA preferred term (PT). The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC. Treatment-emergent SAEs leading to study drug discontinuation will also be summarized by SOC and PT.

Treatment emergent AESI and SAEs will also be summarized by maximum relationship to study drug as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum severity and SOC and PT; and by subject number and SOC and PT. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported. The following listings of AEs will be prepared:

- Listing of treatment-emergent serious adverse events.
- Listing of treatment-emergent AESI.
- Listing of treatment-emergent adverse events leading to discontinuation of study drug.

- Listing of treatment-emergent serious adverse events leading to discontinuation of study drug.
- Listing of all deaths.

10.2.4 Adverse Events of Special Interest

Treatment-emergent adverse events of special interest will be summarized as described in Section 10.2.3 and will be based on standardized MedDRA queries (SMQ). Adverse events of special interest in this study are:

- Hypertension

Detailed information about the search criteria are provided in Appendix B.

10.3 Analysis of Laboratory Data

Data collected from the central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses, except for Baseline where SAE-related laboratory assessments on or before the first dose of study drug will be excluded. The clinical laboratory tests listed in Table 2 will be summarized.

Table 2. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Other Laboratory Tests
Hematocrit	Creatinine	Prostate specific antigen
Hemoglobin	Total bilirubin	**Sex Steroids**
Red blood cell count	Albumin	Testosterone
White blood cell count	Aspartate aminotransferase	
Platelet count (estimate not acceptable)	Alanine aminotransferase	
	Alkaline phosphatase	
	Gamma-glutamyl transferase	
	Sodium	
	Potassium	
	Calcium	
	Cholesterol	
	Low-density lipoprotein cholesterol	
	High-density lipoprotein cholesterol	
	Glucose	
	Triglycerides	

Each laboratory variable listed above will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for laboratory variables listed above, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard deviation, and 95% confidence interval will be presented.

Changes in laboratory parameters will be tabulated using shift tables by categorization of low, normal, or high based on the normal ranges of the laboratory used for each sample. A shift table from baseline to minimum and maximum value (based on normal range), will be created. A similar shift table will be provided to summarize shifts from baseline to the final post-baseline value.

10.4 Analysis of Vital Signs

Vital sign variables include, but are not limited to, SBP and DBP by office measurement, HR, respiratory rate (RR), and oral body temperature.

Each vital sign variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for each vital sign variable, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard deviation, and 95% confidence interval will be presented.

11.0 Interim Analyses

With a sample size of 171 subjects in the per protocol population, the study is powered at 90% if the SD of the change from baseline in average 24-Hour SBP is 10 mmHg.

In order to ensure the assumption of SD holds for the study, a review and estimate of the SD of the change from Baseline to EOT in average SBP from 24-hour recording will be conducted in a blinded fashion when approximately 70% of the planned subjects in the per protocol population (i.e., 120 subjects) have completed the EOT visit. The objective of analysis is to re-estimate sample size if needed. A study database snapshot will be performed for this analysis. The sample size will be re-estimated with updated assumption of SD if necessary. The blinded sample size re-estimation (BSSR) analysis will be performed by an AbbVie statistician external to the study team who has access to unmasked Week 16 ABPM data.

Since the study team is masked to the ABPM data during the study and only SD is used in the sample size re-estimation, no multiplicity adjustment is needed for the BSSR.

Detailed Methodology for BSSR

The initial sample size N_0 is determined by

$$N_0 = \frac{[\, t_{N_0-1}(1-\alpha) + t_{N_0-1}(1-\beta)]^2}{(\mu_0 - B)^2}\hat{\sigma}_e^2$$

Where $t_n(\gamma)$ is the γ-quantile of the *t*-distribution with degree of freedom *n.* α is the one-sided type I error, $1-\beta$ is the power, B is the non-inferiority margin, μ_0 is assumed true change in average 24-hour SBP from Baseline to EOT, and $\hat{\sigma}_e^2$ is the variance estimate of the change from baseline to EOT in average 24-hour SBP. When $\alpha = 0.025$, $1-\beta = 0.9$, $\mu_0 = 0.5$, $B = 3$, SD of change in average 24-hour SBP from Baseline to EOT = 10 ($\hat{\sigma}_e^2 = 10^2 = 100$), then $N_0 = 171$.

Interim BSSR will be conducted when change from baseline to EOT systolic ABP data for the first n_1 (e.g., $n_1 = 120$) subjects are available. Variance of change from baseline to EOT in systolic ABP will be estimated based on n_1 subjects with the formula below.

$$\hat{\sigma}_{os}^2 = \frac{1}{(n_1 - 1)}\sum_{i=1}^{n_1}(d_i - \bar{d})^2$$

where d_i = change from baseline to EOT in average 24-hour SBP for subject *i*, $\bar{d}$ is the mean for all d_i, *i* = 1, ...n_1.

Then the estimated sample size will be calculated as

$$\widehat{N} = \frac{[\, t_{\widehat{N}-1}(1-\alpha) + t_{\widehat{N}-1}(1-\beta)]^2}{(\mu_0 - B)^2}\hat{\sigma}_{os}^2$$

with $\alpha = 0.025, 1-\beta = 0.85, \mu_0 = 0.5, B = 3$.

In order to incorporate a cap of 210 on the sample size (i.e., $N_{cap} = 210$), the final recalculated sample size will be

$$\widehat{N}_{recal} = \min(\max(N_0, \widehat{N}), N_{cap})$$

Based on the formula above, the final recalculated sample size will be always greater than or equal to the initial sample size of 171 evaluable subjects and less than or equal to the limit of 210 evaluable subjects.

The final total sample size will be calculated based on the final recalculated sample size and the current actual rate of loss of subjects from per protocol population.

Interim Database Lock

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

12.0 Overall Type-I Error Control

This study has one primary endpoint for which non-inferiority is tested, so no adjustment for multiple endpoints is needed. Analytically and through simulations, it has been shown that BSSR procedures do not meaningfully affect Type I error rate.[4] Therefore, no multiplicity adjustment is planned for the BSSR analysis.

13.0 Version History

Table 3. SAP Version History Summary

Version	Date	Summary
1.0	24 Mar 2020	Original Version
2.0	14 August 2020	Model for primary safety analysis updated per FDA suggestion. Sensitivity analyses using multiple imputation added per FDA suggestion; sensitivity analysis using linear mixed model updated per FDA suggestion. Pooling strategy for study centers added for clarification. Strata of ongoing medical history of hypertension added as a factor to models of primary, sensitivity, and supportive analyses. Analyses using linear regression model added for other ABPM parameters including daytime SBP/DBP/MAP, nighttime SBP/DBP/MAP, and 24-hour DBP/MAP, per FDA suggestion. Additional subgroup analyses added per FDA suggestion.

14.0 References

1. Available from: https://www.census.gov/geographies/reference-maps/2010/geo/2010-census-regions-and-divisions-of-the-united-states.html.
2. SAS Institute Inc. SAS/STAT® 14.1 User's Guide, The MI Procedure. Cary, NC: SAS Institute Inc. 2015.
3. SAS Institute Inc. SAS/STAT® 14.1 User's Guide, The MIANALYZE Procedure. Cary, NC: SAS Institute Inc. 2015.
4. Kieser M, Friede T. Simple procedures for blinded sample size adjustment that do not affect the type I error rate. Stat Med. 2003;22(23):3571-81.

Appendix A. Protocol Deviations

The number and percentage of subjects who reported at least one of the following protocol deviation categories will be provided.

- Subject entered into the study even though he did not satisfy entry criteria.
- Subject developed withdrawal criteria during the study and was not withdrawn.
- Subject received wrong treatment or incorrect dose of study.
- Subject took prohibited concomitant medication.

Appendix B. Definition of Adverse Events of Special Interest

The following AESI will be collected during the study:

Table 4. Adverse Event of Special Interest

Area of Safety Interest	Search Criteria	
Hypertension	Narrow	Hypertension (SMQ 20000147)