STATISTICAL ANALYSIS PLAN

PROTOCOL AVB244-003

A Prospective, Vehicle Controlled, Double Blinded, Multicenter, Randomized, Phase II Study of B244 Delivered as a Topical Spray to Determine Safety and Efficacy in Subjects with Elevated Blood Pressure

Protocol Number:	AVB244-003
Protocol Version and Date:	Protocol Amendment 3: 30 November 2016
Name of Test Drug:	B244
Indication:	Hypertension
Phase:	Phase II
Methodology:	Prospective, Vehicle Controlled, Double Blinded, Multicenter, Randomized, 2-Arm
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Analysis Plan Date:	19 June 2017
Analysis Plan Version:	Final Version 1.0

APPROVAL SIGNATURE PAGE

Protocol Title:	A Prospective, Vehicle Controlled, Double Blinded, Multicenter, Randomized, Phase II Study of B244 Delivered as a Topical Spray to Determine Safety and Efficacy in Subjects with Elevated Blood Pressure
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Principal Biostatistician

Signature: _____

Date: June 21 2017

Sponsor Approval:

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

Spiros Jamas, ScD
Head of Therapeutics

Signature: _____

Date: 6/20/2017

REVISION HISTORY

Version Number	Version Date	Summary and Rational of Revision(s)
1.0	19 June 2017	This is the first version.

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TABLES AND FIGURES INCLUDED IN THE TEXT

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ABP	Ambulatory blood pressure
ABPM	Ambulatory blood pressure monitoring
ABPP	Ambulatory blood pressure population
AE	Adverse event
AIC	Akaike information criterion
ANCOVA	Analysis of covariance
AOB	Ammonia oxidizing bacteria
AR(1)	First order autoregressive process
ATC	Anatomic therapeutic class
BMI	Body mass index
CI	Confidence interval
CSR	Clinical study report
eCRF	Electronic case report form
ICH	International Conference on Harmonisation
IP	Investigational product
ITT	Intent-to-treat
LS	Least-squares
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects model repeated measures
NO/NO_x	Nitric oxide
PP	Per protocol
Rel Day	Relative study day
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SEM	Standard error of the mean
SOC	System organ class
TEAE	Treatment-emergent adverse event
US	United States
WHO	World Health Organization

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

B244 has been developed as a topical application of a natural source of Ammonia oxidizing bacteria (AOB) and nitric oxide (NO/NO_x) to the human skin. The active ingredient in B244 is available to consumers as a cosmetic product.

Hypertension is one of the most common conditions seen in primary care. About 29% or 1 in 3 American adults have elevated blood pressure (Nwankwo et al, 2013). It increases the risk of stroke, heart and kidney disease and is one of the leading causes of death in the United States (US). However, less than 52% of the affected population control their blood pressure (Mozzafarian et al, 2015) with existing therapeutic options. There is a need for a new modality to control blood pressure with with a benign side effect profile.

B244 was developed as a 'live topical' to provide a natural source of AOB and NO/NO_x to the human skin.

The purpose of this study is to evaluate and compare the efficacy of B244 in treating patients with hypertension.

1.1.2. Study Objectives

1.1.2.1. Primary Objectives

- To evaluate the safety and tolerability of B244 in participants with pre- and Stage I hypertension.
- To assess the efficacy of B244 versus vehicle in reducing in-clinic systolic blood pressure in participants with pre- and Stage I hypertension.

1.1.2.2. Secondary Objectives

- To assess the efficacy of B244 versus vehicle in reducing in-clinic diastolic blood pressure in participants with pre- and Stage I hypertension.
- To assess the efficacy of B244 versus vehicle in reducing mean ambulatory systolic daytime blood pressure.
- To assess the efficacy of B244 versus vehicle in reducing mean ambulatory diastolic daytime blood pressure.
- To assess the efficacy of B244 versus vehicle in reducing mean ambulatory nighttime blood pressure.
- To assess the efficacy of B244 versus vehicle in reducing mean 24-hour blood pressure.

1.1.2.3. Exploratory Objectives

- To evaluate if B244 administration on the skin twice daily for 28 days will affect the levels of inflammatory biomarkers. To explore microbial content, microbiota composition, and B244 presence/absence at baseline and Day 28.
- To evaluate the difference between daytime and nighttime ambulatory blood pressure (ABP).

- To explore and compare the blood pressure change in different ethnic groups, including African-American, Caucasian, Asian, and Hispanic.

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to answer the study objective(s). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

1.2. Study Design

1.2.1. Synopsis of Study Design

This is a prospective, vehicle controlled, double blinded, multicenter, randomized Phase II trial, comparing the effect of twice daily B244 application for 4 weeks versus vehicle application on blood pressure and inflammatory biomarkers.

Patients who have clinically confirmed diagnosis of systolic pre-hypertension and Stage 1 systolic hypertension are eligible for enrollment. Patients must be in general good health as determined by a thorough medical analysis.

It is estimated that 116 participants will be consented in order to provide 104 completed participants for randomization, treatment, and inclusion in the primary analysis.

After screening and recruitment, participants will be randomized to active or vehicle B244 application for 28 days. Subjects will apply investigational product (IP) twice-a-day as follows:

- Study Arm 1: 4 pumps to the face
- Study Arm 2: 4 pumps to the face and 4 pumps to the torso

Clinical assessments of response to treatment will be made at Study Day 1 (baseline) and Study Days 7, 14, 21, 28 and 42.

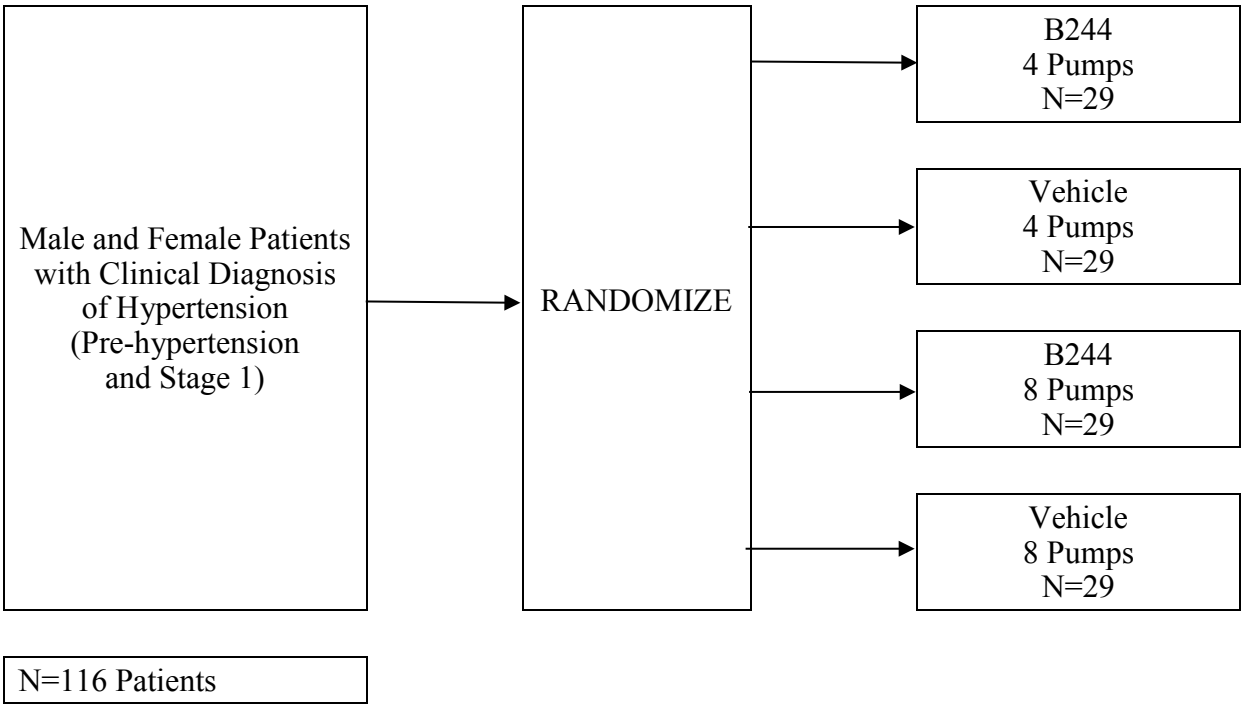
Safety evaluations will consist of review of participant's medical history at screening and ongoing assessment of adiverse events (AEs) reported throughout the study duration.

1.2.2. Randomization Methodology

Randomization will be evenly allocated across 2 dosing applications (4 pumps or 8 pumps) and 2 treatments (B244 or placebo) and stratified by hypertension status, so that equal numbers of patients will be treated in each of the 4 treatment groups of the study. All B244 randomized subjects will be treated at the dose of 8×10^9 cfu/ml.

The study schema is illustrated in Figure 1.

Figure 1: Study Schema



1.2.3. Stopping Rules and Unblinding

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator.

Reasons for withdrawal (participants who refuse to complete any remaining study visits) or discontinuation (participants who prematurely stop the application) at any time during the study may include, but are not limited, to the following:

- For safety reasons, either at the discretion of the Investigator or at the participant's request.
- For protocol violations at the discretion of AOBiome.
- Due to concomitant therapy that could interfere with the results of the study (the Investigator will report all such information on the CRFs and decide, in accordance with AOBiome, whether the participant is to be withdrawn).

The reason for participant study withdrawal will be recorded on the electronic Case Report Form (eCRF). Data from participants withdrawing from the study will be considered evaluable up to the point at which they are withdrawn using the same criteria for evaluability as for participants who complete the study.

The Investigator may unblind a participant's treatment assignment only in the case of emergency or in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant, as determined by the Investigator. It is preferred (but not required) that the Investigator first contact the Medical Monitor to discuss options before unblinding the participant's treatment assignment. The Investigator must notify the Sponsor as soon as possible when a participant's treatment assignment is unblinded without revealing the treatment assignment of the unblinded

participant unless that information is deemed important for the safety of participants currently in the study. The date and reason for the unblinding must be documented in the participant's study record.

The Medical Monitor may unblind the treatment assignment for any participant with a serious adverse event (SAE). If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to clinical investigators in accordance with local regulations and/or sponsor policy.

1.2.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, is presented in Table 1. The study flow is presented in Table 2.

Table 1: Schedule of Assessments

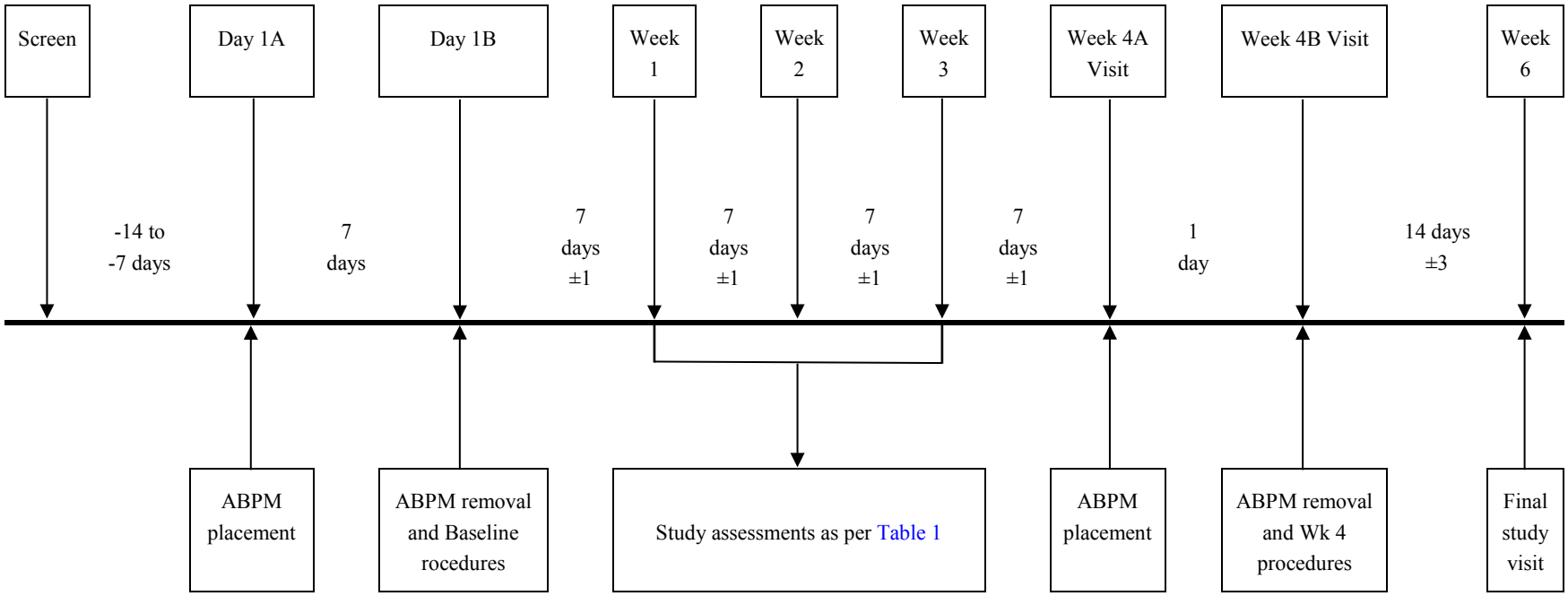
Visit Name (Day)	Screening (Day 0)	Day 1A	Day 1B	Visit 1R	Week 1 (Day 7)	Week 2 (Day 14)	Week 3 (Day 21)	Week 4A (Day 28)	Visit 4B	Visit 4R	Week 6 (Day 42)	Unscheduled Visit
Visit Window in Days	**-14 to -7**	**-7 to -1**	**-1 to 0**		**+/-1**	**+/-1**	**+/-1**	**+/-1**	**+/-1**		**+/-3**	
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Demographics	X											
Medical History	X											
Concomitant Medications	X				X	X	X	X			X	X
Smoking Status	X											
Physical Exam	X											X
Body Weight	X				X	X	X	X			X	
Height	X											
12-Lead ECG	X							X				X
Clinical Chemistry[1, 2]	X							X				
Blood for Biomarkers[3]			X			X		X				X
In-Clinic BP and HR	X	X			X	X	X	X			X	X
Urine Pregnancy Test for WOCBP[4]	X											
ABPM placement[5]		X		X				X		X		
ABPM Removal			X	X					X	X		
IWRS			X									
Dispense Investigational Product to Patient			X									
Investigational Product Application[6]			X		X	X	X	X	X[7]			

Visit Name (Day)	Screening (Day 0)	Day 1A	Day 1B	Visit 1R	Week 1 (Day 7)	Week 2 (Day 14)	Week 3 (Day 21)	Week 4A (Day 28)	Visit 4B	Visit 4R	Week 6 (Day 42)	Unscheduled Visit
Visit Window in Days	**-14 to -7**	**-7 to -1**	**-1 to 0**		**+/-1**	**+/-1**	**+/-1**	**+/-1**	**+/-1**		**+/-3**	
Investigational Product Compliance[8]			X		X	X	X	X	X			X
Counseling[9, 10]		X	X		X	X	X	X				
Soap and Shampoo[11]			X		X	X	X	X	X[7, 12]			
Study Diary[13]			X		X	X	X	X				X
Skin Swabs[14]			X					X			X	X
AEs[15]			X		X	X	X	X			X	X

Abbreviations: ABPM=Ambulatory blood pressure monitoring, AE=Adverse event, BP=Blood pressure, ECG=Electrocardiogram, IWRS=Interactive web response system, HR=Heart rate, IP=Investigational product, WOCBP=Woman of child-bearing potential.

1. Patients should fast for at least 8 hours before the test. Blood for clinical chemistry will be shipped to the central lab for processing.
2. Blood for HbA1C only will be drawn at the Week 4A visit and shipped to central lab or processing.
3. Blood samples for biomarkers will be collected and processed on site. Patients should fast for at least 8 hours before the test. Samples will then be frozen onsite and shipped on monthly bases to the Central lab for storage.
4. Urine pregnancy test for WOCBP will be done at Screening.
5. If subject undergoes ABPM procedures and equipment fails, subject will be scheduled for another ABPM session within 48 hours for Visit 1R or 4R.
6. Subjects will be asked to apply the IP twice daily as per their randomization. First IP application will happen in the office under medical supervision.
7. In the event that subject fails the ABPM test on Visit 4B and needs to repeat it, subject should continue applying the IP through Visit 4R. Investigational product and soap/shampoo should be returned to the site on Visit 4R. Every effort should be made by the site to schedule Visit 4R as close to Visit 4B as possible.
8. Weight of an IP kit will be obtained at the at the 1B visit. Weight of an individual bottle that is currently in use will be obtained at each visit. Final weight of the kit will be obtained at Week 4B visit, when kit is returned by the patient.
9. Subjects will be counseled on the use of study medication, diary and answer any questions subject may have.
10. Subjects will be counseled on the use of ABPM equipment.
11. Subjects are to be provided soap and shampoo at Baseline visit. However, soap and shampoo is available upon request in the event that subjects run out of their initial supplies.
12. Soap and shampoo should be returned to the Study Coordinator.
13. Subjects will be asked to fill out study diary for the duration of the study (Baseline-Day 28).
14. Skin swabs will be obtained during the office visit and will be frozen in the -80 freezer and will be shipped monthly to Biostorage labs.
15. AEs will be monitored throughout the trial.

Table 2: Study Flow



1.2.5. Efficacy Parameters

- Difference in mean in-clinic systolic blood pressure between the active and vehicle groups.
- Difference in mean in-clinic diastolic blood pressure between the active and vehicle groups.
- Difference in mean ambulatory systolic and diastolic blood pressure.

1.2.6. Safety Parameters

Safety and tolerability endpoints will consist of all adverse events (AEs) reporting during the study duration.

1.2.7. Exploratory Parameters

- Difference in inflammatory biomarkers between active and vehicle groups.
- Microbial content, microbiota composition, and B244 presence/absence at baseline and Day 28.

2. SUBJECT POPULATION

2.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

- Intent-to-Treat (ITT) Population: Includes all randomized participants. Subjects will be analyzed according to the treatment assigned by the randomization schedule. The ITT population will be the primary population for efficacy analyses.
- Safety Population: Includes all subjects who received at least 1 dose of study medication. Subjects will be analyzed according to the study drug received.
- Per Protocol (PP) Population: Subjects who have baseline and Day 28 post-baseline in-clinic systolic or diastolic blood pressure measurement, and did not have any major protocol violations which could potentially compromise interpretation of results. The PP population will be used for supportive summaries of efficacy data.
- Ambulatory Blood Pressure Monitoring Population (ABPP): Subjects in the Safety population who had valid baseline and Day 28 ambulatory blood pressure monitoring (ABPM) measurements. Subjects who repeated the ABPM are included in the population if the repeated assessment met the device monitor's criteria for "passing."

The ITT population is the primary population for the analysis of efficacy parameters. A subset of efficacy parameters will be evaluated for the PP population (see Section 4.3). The Safety population is the primary population for the analysis of safety endpoints.

2.2. Protocol Violations

All the following deviations will be summarized on the ITT patient population and may include:

- Inclusion or exclusion criteria not satisfied.
- Deviations related to the IP administration.
- Repeated use of soap or shampoo other than the products provided by AOBIOME.

At the discretion of the Sponsor, major protocol violations, as determined by a review of the data prior to unblinding of the study results and the conduct of statistical analyses, may result in the removal of a subject's data from the PP population. The Sponsor or designee will be responsible for producing the final protocol violation file (formatted as a Microsoft Excel file), in collaboration with Veristat and the data monitoring group as applicable; this file will include a description of the protocol violation and clearly identify whether or not this violation warrants exclusion from the PP population. This file will be finalized prior to hard database lock.

All protocol violations will be presented in a data listing.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

A total sample size of 116 randomized subjects, divided into 2 arms (placebo or B244)) of 58 subjects each allows for a dropout rate of 10%. It is expected that each strata will have at least 52 subjects with sufficient data needed determine the effect of the IP on blood pressure.

With the planned number 52 subjects per arm, the study is powered 80%, to detect a treatment effect = 5.8 (mean change in systolic blood pressure from baseline), standard deviation (SD) = 10.5 (higher SD than was observed in Phase 1b/2a) ,with alpha = 0.05, using a 2-sample t-test.

Based on the above sample size, the study is powered 90% to detect the treatment effect of 5.8 (mean change in systolic blood pressure from baseline) and SD = 9, using a 2-sample t-test, that was observed in the Phase 1b/2a study.

In the planned analyses, mixed models will be used to account for the correlation of the assessments over time and provide a more robust analysis of the endpoint.

3.2. General Methods

The analyses will be conducted on all participant data when the trial ends. Data will be presented by treatment arm and overall except where noted. Listings will be sorted by treatment, strata, and subject.

Analysis of the change from baseline in systolic and diastolic blood pressure will be performed using a both mixed-effects model repeated measures (MMRM) and an analysis of covariance (ANCOVA). Least squares (LS) means, confidence interval (CI) on the means, and p-values from the model will be presented. In addition, descriptive statistics on the actual values and the change from baseline will be presented for the 4-spray B244 arm, the 8-spray B244 arm, and the placebo arm.

Categorical variables will be summarized by frequency distributions (number and percentages of subjects) and continuous variables will be summarized by descriptive statistics (mean, SD, etc).

Adverse events will be summarized by treatment using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term. Separate tabulations will be produced for all treatment-emergent AEs (TEAEs), treatment-related AEs (those considered by the Investigator as at least possibly drug-related), and AEs with Grade 3 or higher severity. By-subject listings will be provided for any deaths, SAEs, and AEs leading to discontinuation.

Descriptive statistics for each treatment arm will be provided for clinical laboratory values (eg, serum chemistry) and vital signs data, presented as both actual values and changes from baseline relative to each on-study evaluation. Out of range clinical laboratory values will be listed.

All data will be provided in by-subject listings.

All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study medication which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc.

All output will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, SD, minimum, and maximum values will be presented.

Formal statistical hypothesis testing will be performed on the primary and secondary efficacy endpoints with all tests conducted at the 2-sided, 0.05 level of significance. Comparisons of baseline characteristics will be performed in order to assess comparability of the treatment arms. Summary statistics will be presented, as well as 2-sided 95% CIs on selected parameters, as described in the sections below. P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as <0.0001 and p-values that round to 1.00 will be presented as >0.9999.

3.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software v9.3 unless otherwise noted. Medical history and AEs will be coded using MedDRA v19.0. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary March 2016.

3.4. Baseline Definitions

For all analyses, baseline will be defined as the most recent measurement prior to the first administration of study drug. Unless otherwise noted below, measurements collected on Day 1A meet this criteria.

3.5. Methods of Pooling Data

Data will be pooled by site for all analyses. With the exception of disposition and baseline tabulations, summary data will be pooled for subjects who received placebo.

3.6. Adjustments for Covariates

Exploratory analyses will include baseline covariates which may impact the response to treatment and will include race (Black/African-American vs Non-Black/African-American), body mass index (BMI) category, and smoking status (current vs other).

3.7. Multiple Comparisons/Multiplicity

Analyses will not be adjusted for multiple endpoints.

3.8. Subpopulations

In-clinic and ambulatory systolic and diastolic blood pressure results will be reported separately for Black/ African-American subjects, pre-hypertensive and Stage 1 hypertensive subjects, age, and sex (male/female). In addition, blood pressure results may be analyzed according to dipper/nondipper ambulatory blood pressure at screening. Nondippers are defined as subjects who have <%10 decrease in nighttime systolic blood pressure compared to daytime systolic blood pressure.

3.9. Withdrawals, Dropouts, Loss to Follow-up

Subjects who drop out after enrollment but prior to randomization will be replaced.

3.10. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the eCRF will be included in data listings that will accompany the CSR.

When tabulating AE data, partial dates will be handled as follows. If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of treatment. If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment in order to conservatively report the event as treatment-emergent. A missing onset date will be coded as the day of treatment.

In all cases, the resulting date will be compared to the AE end date, if present. If the imputed start date is later than the AE end date, then the start date will be set equal to the end date. The imputed start date is used only for determining treatment emergence; data listings will present the partial date as recorded on the eCRF.

For the primary and secondary efficacy endpoints, the primary analysis will be based on the MMRM method, which makes use of fully and partially observed data sequences from individual patients by estimating the covariance between data from different time points. Treatment group means are adjusted to reflect both the actually observed data and the projected outcomes from the patients with missing data.

3.11. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the CRF even if the assessment is outside of the protocol-sprecified visit window.

3.12. Interim Analyses

No interim analyses are planned for this study.

4. STUDY ANALYSES

4.1. Subject Disposition

A tabulation of the disposition of subjects will be presented by dose assignment and overall. The number enrolled, the number randomized, the number treated in each arm, the number in each strata, and the reasons for study discontinuation will be reported. Summaries of the number in each analysis set will be summarized. Entry criteria and protocol deviations will be listed. Screen failures will be listed.

A by-subject data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented.

4.2. Demographics and Baseline Characteristics

Demographic and baseline characteristic data summarization will be performed in order to descriptively assess the comparability of strata and treatments. Summaries will be performed on the ITT and PP populations. Data to be tabulated will include age, sex, race, ethnicity, BMI, and smoking history as well as baseline characteristics related to medical history. BMI and age will be analyzed as a continuous variable using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Sex, race, ethnicity, BMI category (<30 kg/m^2, ≥ 30 kg/m^2), smoking status, and age category (<60 years, ≥ 60 years) will be summarized by frequency (count and percent). Selected baseline variables will be compared to assess the balance of characteristics across the treatment groups. Age and BMI will be compared using ANCOVA and sex, race, and smoking history will be compared using a Cochran-Mantael Haenzel test.

Demography, general and targeted medical history, and smoking history will be presented in data listings.

4.3. Efficacy Evaluation

The primary endpoint in this trial is the decrease in in-clinic systolic blood pressure from Baseline (Day 1A) through Day 28. Durability of the blood pressure change will evaluated at Day 42 , when subjects have discontinued use of IP for at least 14 days.

All evaluations described below will all applied to both systolic and diastolic blood pressure.

4.3.1. Weekly In-Clinic Blood Pressure

To assess treatment effect, change from baseline in weekly systolic and diastolic blood pressure values will be analyzed using a mixed effect model that includes the change from baseline at Days 7, 14, 21, and 28. Day 42 will not be used in the primary endpoint analysis. The model will include stratification factors of spray number and hypertension and baseline blood pressure as covariates, with treatment group (B244 or placebo) and visit as fixed effects, and subject as a random effect. The model will include the following interaction terms: treatment*visit, strata*visit, treatment*strata, and treatment*strata*visit. Estimates of the adjusted LS mean, difference in LS means, and corresponding 95% CIs will be obtained from the model.

Linear contrasts of the differences between each treatment group (4 doses or 8 doses) and placebo at each visit will be used to compare the results between treatments using LS means between each active treatment group and placebo. Nominal 2-sided p-values and 95% CIs will be reported at Days 7, 14, 21, and 28.

Treatment group comparisons within each strata will be an exploratory analysis.

Mixed models will be implemented using PROC Mixed in SAS, using an unstructured within-subject covariance matrix and denominator degrees of freedom from the Kenward-Roger method. Other covariance matrices (first order autoregressive process [AR(1)], compound symmetry, independent) may be utilized in the event that the unstructured matrix does not converge. In this event, the matrix structure that converges provides the lowest akaike information criterion (AIC) value will be selected.

This modeling will be performed for both systolic and diastolic blood pressure, in both the ITT and PP populations.

In addition to the model results, descriptive statistics will be presented by treatment for actual value and change from baseline at each visit (Days 0, 7, 14, 28, and 42). Tabulations will be performed for both the ITT and PP populations. Statistics will also be presented for the subgroups of African-American/non-African-American, pre-hypertension/Stage 1 hypertension, male/female, and age <60/ ≥60 subjects in the ITT population. Additionally the mean difference between the active treatment group and the placebo for each category of the subgroup along with the 95% confidence interval and p value will also be presented. In addition, mixed model analyses of change from baseline will be performed separately for the pre-hypertensive and Stage 1 subjects using both ITT and PP populations.

4.3.1.1. Supportive Analysis: Analysis of Covariance

An additional analysis of change from baseline at Day 28 will be performed using the ANCOVA model for the ITT and PP populations. This model will include the change from baseline at Day 28, strata, and treatment group (plus an interaction term strata*treatment).

4.3.2. Graphical Analysis of Weekly In-clinic Blood Pressure

Mean blood pressure (± standard error of the mean [SEM]) at each visit will be graphed with separate lines for each treatment group. In addition, the mean (SEM) change from baseline will be graphed. Least squares means will be graphed in similar fashion.

4.3.3. Ambulatory Blood Pressure

The analysis of ABP will be modeled in 3 ways. The first will compare the change in average daytime (8 AM to 4 PM) values of diastolic and systolic blood pressure at baseline to the average values post-baseline using an ANCOVA model with stratification and treatment included in the model. Means and LS means will be reported. All analyses will be performed using the ABPM population.

In addition to the results of the model, mean hourly results, daytime(8 AM to 4 PM), nighttime (10 PM to 6 AM), and 24-hour results will be summarized by treatment group.

This ANCOVA model will also be performed separately for the pre-hypertensive and Stage 1 subjects.

The second method will use piecewise linear functions (linear splines) in which linear slopes of each subject's values over time at baseline and post-baseline periods are calculated. The first "knot" will be placed at the time of treatment and additional knots will be evaluated graphically using lowess smoothing curve graph to determine a second inflection point of non-linearity. By calculating the coefficient of each spline, the rate of change in ABP can be calculated and compared between treatment groups.

ABP will also be analyzed by Dippers and Non-Dippers based on the American Heart Association classification using systolic blood pressure. Dippers and Non-Dippers are defined as follows:
Dipper: ≥10% decrease in nighttime ambulatory SBP versus daytime ambulatory SBP.
Non-Dipper: <10% decrease in nighttime ambulatory SBP versus daytime ambulatory SBP.

The shift in dipping classification from baseline to day 28 will be tabulated.

4.3.4. Graphical Analysis of Ambulatory Blood Pressure

Mean blood pressure (± SEM) at each hour, daytime, nighttime , and 24-hours at baseline and Day 28 will be graphed with separate lines for each treatment group. Least squares means will be graphed in similar fashion.

4.3.5. Exploratory Analyses

The influence of baseline factors such as race may be included in the models described in Section 4.3.1 if sufficient data are available for secondary analyses.

4.4. Safety Analyses

Safety analyses will be conducted using the Safety population.

4.4.1. Study Drug Exposure

The cumulative amount of study drug exposure will be estimated by calculating the difference between the weight of the 4 bottles of drug at the time the drug was dispensed and the weight of the 4 bottles at the last visit. The amount of product used per day will be estimated by dividing the change by the number of days the subject was on treatment. These weights will be compared to the weight of the product that would be used if the subject was compliant with the protocol and used the spray 4 or 8 times per day for 28 days.

Percent compliance will be summarized for each subject from date of first dose through the treatment period based on the net weight of the product administered. Net weight is calculated as the weight collected at Day 29 (or Day 28 , if the subject stopped using the study drug at the visit prior to ABPM placement) minus the weight at Day 1. Based on information provided by AOBiome, the expected amount of study drug used per week is approximately 7.91 g/week for 4 sprays/application and 15.82 g/week for 8 sprays/application.

$$= \frac{(\qquad\qquad)}{(\qquad 28 \qquad)} \times 100$$

The number of days the subject administered study drug, the amount of product used, and the percent compliance will be summarized by treatment group and presented in a by-subject data listing. The subject listing will also include by-visit IP weights. Percent compliance will be calculated only for subjects who returned the study drug at Day 28 or Day 29. In the listing, subjects who withdrew from the study early will be flagged.

4.4.2. Adverse Events

Adverse events will be analyzed in terms of treatment-emergent adverse events (TEAEs) which are defined as any AEs that begin or worsen on or after the start of study drug through 30 days after the last dose of study drug.

A treatment-related TEAE is defined as a TEAE that was considered by the Investigator to be at least possibly related to the study drugs.

If a subject experiences the same AE more than once with different toxicity grades, the event with the highest grade will be tabulated in the "by grade" tables. If a subject experiences multiple AEs under the same preferred term (SOC), the subject will be counted only once for that preferred term (SOC). In addition, AEs with a missing severity will be presented in the summary table as an intensity category of "Missing."

An overall summary table presenting the number of subjects who experienced the following will be presented by treatment arm: any AE, any related AE, any severe AE, any serious AE, any serious related AE, any AE leading to discontinuation of study drug, and any AE leading to study discontinuation.

The incidence of TEAEs will be summarized by MedDRA SOC and preferred term. Tables summarizing the incidence of TEAEs will be generated for each of the following:

- All TEAEs
- TEAEs reported as treatment-related
- Severe or Grade 3/4 TEAEs

If no subjects experience any of the events in the overall summary table, the corresponding table by SOC and preferred term will not be produced.

No formal hypothesis-testing analysis of AE incidence rates will be performed.

All AEs occurring on-study will be listed in subject data listings.

By-subject listings also will be provided for the following: subject deaths, serious AEs, and AEs leading to withdrawal.

4.4.3. Laboratory Data

Clinical laboratory values will be expressed in the units reported by the central laboratory.

The actual value and change from baseline (Day 1) to Day 28 will be summarized for each clinical chemistry parameter. In the event of repeat values, the last non-missing value per visit will be used.

All laboratory data will be provided in data listings. Values outside of the lab parameter's normal range will be flagged as high, low, or abnormal based on the range of the test.

4.4.4. Vital Signs and Physical Examination

Vital sign measurements will be presented for each subject in a data listing. Systolic blood pressure, diastolic blood pressure, heart rate, and weight will be summarized as actual value and change from baseline by visit. If the safety population is identical to the ITT population, summaries of blood pressure will not be included in these tables because this will be produced for the primary endpoint as described under the efficacy analysis.

All physical examination findings will be presented in a data listing.

4.4.5. Electrocardiogram

Electrocardiogram results will be summarized descriptively, including the number and percentage of subjects with normal, abnormal, and clinically significant abnormal results at baseline and at Day 28.

Electrocardiogram data for each subject will be provided in a data listing.

4.4.6. Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary. Results will be tabulated by anatomic therapeutic class (ATC) and preferred term.

Concomitant medications will be tabulated by treatment group, where any medications that did not end prior to first dose will be included. If an end date is missing or the medication is ongoing, the medication will be included.

The use of concomitant medications will be included in a by-subject data listing.

5. CHANGES TO PLANNED ANALYSES

The following changes between the study protocol are described below.

Editorial edits have been made in Section 1.1.1 (Introduction), Section 1.2.1 (Synopsis of Study Design), Section 1.2.2 (Randomization Methodology), and Section 1.2.5 (Efficacy Parameters) to clarify the information from the study protocol.

The schedule of events was changed according to an administrative letter from AOBiome dated 08 February 2017. Subjects were instructed to continue use of IP through end of the ABPM monitoring period (Day 29 [Visit 4B] and to weigh the IP after this visit. Subjects who had already completed the Day 29 visit prior to the notification should have used the IP through Day 28 and weighed the product on this visit.

The SD in the sample size was changed from 11 to 10.5 in order to estimate power correctly.

6. REFERENCES

Nwankwo T, Yoon SS, Burt V, Gu Q. Hypertension among adults in the US: National Health and Nutrition Examination Survey, 2011-2012. NCHS Data Brief, No. 133. Hyattsville, MD: National Center for Health Statistics, Centers for Disease Control and Prevention, US Dept of Health and Human Services, 2013.

Mozzafarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics-2015 Update: a report from the American Heart Association.Circulation. 2015;e29-322.

7. STATISTICAL OUTPUT

7.1. List of Statistical Output

GENERAL PROGRAMMING NOTES:

1. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented.
2. For continuous variables, the number of subjects, mean, median, SD, minimum, and maximum values will be presented.
3. Formal statistical hypothesis testing will be performed on the primary and secondary efficacy endpoints with all tests conducted at the 2-sided, 0.05 level of significance.
4. P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as <0.0001 and p-values that round to 1.00 will be presented as >0.9999.

7.1.1. Statistical Table Shells

The following tables will be produced.

STATISTICAL TABLES

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Table 14.1.1

Subject Enrollment and Disposition (All Enrolled Subjects)

		B244		Placebo		
Disposition	Statistic	4 Sprays (N=xx)	8 Sprays (N=xx)	4 Sprays (N=xx)	8 Sprays (N=xx)	Overall (N=xx)
Total Number of Subjects						
Screened	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Screen Failures [1]	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Enrolled [1]	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Randomized [1]	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treated [2]	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed the Study [3]	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study Population [4]						
Safety	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Intent-to-Treat (ITT)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Per Protocol (PP)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ambulatory Blood Pressure	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Strata						
Pre-Hypertension	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Stage 1 Hypertension	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason for Early Study Discontinuation						
Death	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to follow-up	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal of consent by subject	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Investigator's decision	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Screen Failure	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[1] Percentage based on the number screened.
[2] Percentage based on the number enrolled.
[3] Percentage and all subsequent percentages based on the number dosed.
[4] Safety Population: All subjects who received at least 1 dose of study medication, analyzed according to drug received.
Intent-to-Treat (ITT) Population: all randomized subjects, analyzed according to treatment assigned.
Per Protocol (PP) Population: Subjects who were administered at least 50% of , have baseline and at least 1 post-baseline in-clinic systolic or diastolic blood pressure measurement, and did not have any major protocol violations which could potentially compromise interpretation of results.
Ambulatory Blood Pressure Monitoring Population (ABPP): Subjects in the Safety population who had valid baseline and Day 28 ABPM measurements. Subjects who repeated the ABPM are included in the population if the repeated assessment met the Monitor's criteria for "passing."
Source: Listing 16.2.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX | DATE: DDMMMYYYY HH:MM

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Table 14.1.2.1A

Demographics and Baseline Characteristics (ITT Population)

		B244		Placebo		
Parameter	Statistic	4 Sprays (N=xx)	8 Sprays (N=xx)	4 Sprays (N=xx)	8 Sprays (N=xx)	Overall (N=xx)
Age (years)	n	xx	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
	P-value [1]					0.xxxx
Age Category (years)						
<60	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>=60	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	P-value [2]					0.xxxx
Sex						
Female	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Male	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	P-value [2]					0.xxxx
Race						
American Indian or Alaska Native	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black or African	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
American	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian or Other Pacific Islander	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
White	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity						
Hispanic/Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic/Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[1] P-value is from ANCOVA model.
[2] P-value is from Cochran-Mantel-Haenszel test.
Source: Listing 16.2.4.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Table 14.1.2.1A

Demographics and Baseline Characteristics (ITT Population)

		B244		Placebo		
Parameter	Statistic	4 Sprays (N=xx)	8 Sprays (N=xx)	4 Sprays (N=xx)	8 Sprays (N=xx)	Overall (N=xx)
Weight (kg)	n	xx	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
BMI (kg/m^2)	n	xx	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
	p-value [1]					0.xxxx
BMI Category (kg/m^2)						
<30	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>=30	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Smoking History						
Never	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Former	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Current	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[1] P-value is from ANCOVA model.
[2] P-value is from Cochran-Mantel-Haenszel test.
Source: Listing 16.2.4.1, Listing 16.2.4.2

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for:
Table 14.1.2.1B Demographics and Baseline Characteristics (PP Population)

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Table 14.1.3.1A

Concomitant Medication by Anatomic Therapeutic Class and Preferred Term (ITT Population)

		B244		Placebo		
Parameter	Statistic	4 Sprays (N=xx)	8 Sprays (N=xx)	4 Sprays (N=xx)	8 Sprays (N=xx)	Overall (N=xx)
ATC 1						
PT 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.						
ATC 2						
PT 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.						
Etc.						

Note: Concomitant medications are any medications that did not end prior to first dose. If an end date is missing or the medication is ongoing, the medication is included.
Note: Concomitant medications anatomic therapeutic class (ATC) and preferred term (PT) are coded using the WHO Drug Dictionary version March 2016.
Source: Listing 16.2.9.4

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for:
Table 14.1.3.1B Concomitant Medication by Anatomic Therapeutic Class and Preferred Term (PP Population)

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Table 14.1.4.1A

Summary of Drug Exposure (ITT Population)

		B244		Placebo		
Parameter	Statistic	4 Sprays (N=xx)	8 Sprays (N=xx)	4 Sprays (N=xx)	8 Sprays (N=xx)	Overall (N=xx)
Cumulative Study Drug Exposure (g) [1]	n	xx	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Amount of Product Used per Day (g) [2]	n	xx	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Days of Study Drug Administration	n	xx	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Percent Compliance [3]	n	xx	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

[1] Cumulative study drug exposure = weight of the 3 drug bottles at last visit - weight of the 4 drug bottles at first dispense.
[2] Amount of product used per day = change / number of days the subject was on treatment.
[3] Percent compliance = (Net weight of study drug) / (Expected net weight for 28 days of use) × 100.
Source: Listing 16.2.5.1, Listing 16.2.5.2

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for:
Table 14.1.4.1B Summary of Drug Exposure (PP Population)

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Table 14.2.1A

Summary of Values and Change from Baseline for Systolic and Diastolic Blood Pressure – Mixed Model Analysis (ITT Population)

Parameter: Systolic Blood Pressure

			B244			
Visit	Actual/ Change	Statistic	4 Sprays (N=xx)	8 Sprays (N=xx)	All B244 (N=xx)	Placebo (N=xx)
Baseline	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Day 7	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
	Change	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
		LS MEAN (SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		95% CI	xx, xx	xx, xx	xx, xx	xx, xx
		LS MEAN Difference B244 – Placebo (SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	
		95% CI	xx, xx	xx, xx	xx, xx	
		P-value [1] (vs Placebo)	0.xx	0.xx	0.xx	
		P-value [1] (vs 8 Sprays)	0.xx			
Day 14		<as above in Day 7>				
Day 21		<as above>				
Day 28		<as above>				
Day 42		<repeat Actual and Change parameters only>				

Note: Day 42 is not included in model.In the mixed-effect model repeated measures (MMRM) model, the outcome variable is change from baseline in NIS-W. The model includes baseline blood pressure as covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction and hypertension status.
[1] P-value is derived from the contrast testing at each visit using the MMRM model.
Source: Listing 16.2.6.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Continue for Diastolic Blood Pressure Mixed Model Analysis.

Repeat Table 14.2.1A for:

Table 14.2.1B Summary of Values and Change from Baseline for Systolic and Diastolic Blood Pressure – Mixed Model Analysis (PP Population)

Table 14.2.1C Summary of Values and Change from Baseline for Systolic and Diastolic Blood Pressure by Race – Mixed Model Analysis (ITT Population)
Table 14.2.1D Summary of Values and Change from Baseline for Systolic and Diastolic Blood Pressure by Hypertension Stage – Mixed Model Analysis (ITT Population)
Table 14.2.1E Summary of Values and Change from Baseline for Systolic and Diastolic Blood Pressure by Gender – Mixed Model Analysis (ITT Population)
Table 14.2.1F Summary of Values and Change from Baseline for Systolic and Diastolic Blood Pressure by Age Group – Mixed Model Analysis (ITT Population)

PROGRAMMING NOTE: Replace Visit with each subgroup as applicable per table title. P-values and LSMEANs are not required for any subgroups except hypertension stage.

Table 14.2.2A

Change from Baseline at Day 28 ANCOVA Model for Systolic and Diastolic Blood Pressure (ITT Population)

Parameter: Systolic Blood Pressure

		B244			
Visit	Statistic	4 Sprays (N=xx)	8 Sprays (N=xx)	All B244 (N=xx)	Placebo (N=xx)
Day 28	LS Mean (SE) 95% CI	xx.x (xx.xx) xx.x	xx.x (xx.xx) xx.x	xx.x (xx.xx) xx.x	xx.x (xx.xx) xx.x
	LS Mean Difference (SE) (Placebo-Active)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	
	95% CI for Mean Difference	Xx, xx	Xx, xx	Xx, xx	
	P-value (vs Placebo)	0.xxxx	0.xxxx	0.xxxx	
	P-value (vs 8 Spray)	0.xxxx			

LS: Least-squares. SE = Standard Error. CI = Confidence Interval.
Model: The ANCOVA model includes the change from baseline as the dependent variable, treatment and strata as factors and baseline value as a covariate.
Source: Listing 16.2.6.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Continue for Diastolic Blood Pressure.

Repeat for:
Table 14.2.2B Change from Baseline at Day 28 ANCOVA Model for Systolic and Diastolic Blood Pressure (PP Population)
Table 14.2.2C Change from Baseline at Day 28 ANCOVA Model for Systolic and Diastolic Blood Pressure by Hypertension Stage (ITT Population)

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Table 14.2.3A

Summary of Values and Change from Baseline for Ambulatory Blood Pressure (ABP Population)

Parameter: Systolic Blood Pressure

Parameter	Visit	Actual/Change	Statistic	4 Sprays (N=xx)	8 Sprays (N=xx)	Placebo (N=xx)
Daytime	Baseline	Actual	n	xx	xx	xx
			Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x	xx.x
			Min, Max	xx, xx	xx, xx	xx, xx
Daytime	Day 28	Actual	n	xx	xx	xx
			Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x	xx.x
			Min, Max	xx, xx	xx, xx	xx, xx
Daytime	Day 28	Change	n	xx	xx	xx
			Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x	xx.x
			Min, Max	xx, xx	xx, xx	xx, xx
Nighttime			n	xx	xx	xx
			Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x	xx.x
			Min, Max	xx, xx	xx, xx	xx, xx
24-hour			n	xx	xx	xx
			Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x	xx.x
			Min, Max	xx, xx	xx, xx	xx, xx

Source: Listing 16.2.6.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Continue for Diastolic Blood Pressure and Mean Arterial Pressure. If the subject has results for more than 24 hours in a visit, only the first time point per hour will be included in the analysis. Repeat Daytime layout for Nighttime and 24-hour analysis.

Repeat for:
- Table 14.2.3B Summary of Values and Change from Baseline for Ambulatory Blood Pressure by Race (ABP Population)
- Table 14.2.3C Summary of Values and Change from Baseline for Ambulatory Blood Pressure by Hypertension Stage (ABP Population)
- Table 14.2.3D Summary of Values and Change from Baseline for Ambulatory Blood Pressure by Gender (ABP Population)
- Table 14.2.3E Summary of Values and Change from Baseline for Ambulatory Blood Pressure by Age Group (ABP Population)

  PROGRAMMING NOTE: Replace Visit with each subgroup as applicable per table title.

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Table 14.2.4A

Mixed Model Analysis of Change from Baseline in Daytime Ambulatory Blood Pressure (ABP Population)

Parameter: Systolic Blood Pressure

		4 Sprays (N=xx)		8 Sprays (N=xx)		Placebo (N=xx)	
Time Point	Statistic	Baseline	Day 28	Baesline	Day 28	Baseline	Day 28
Hour 1	n	xx	xx	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Hour 2	n	xx	xx	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Hour 3	n	xx	xx	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

Source: Listing 16.2.6.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Continue for Diastolic Blood Pressure. If the subject has results for more than 24 hours in a visit, only the first time point per hour will be included in the analysis.

Repeat for:
Table 14.2.4B Mixed Model Analysis of Change from Baseline in Daytime Ambulatory Blood Pressure by Hypertension (ABP Population)
Table 14.2.4C Mixed Model Analysis of Change from Baseline in Daytime Ambulatory Blood Pressure by Age Group (ABP Population)
PROGRAMMING NOTE: Add column for each subgroup as applicable per table title.

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Table 14.2.5

Change in Proportion of Dippers and Nondippers from Baseline to Day 28 Visit (ABP Population)

		Day 28		
Treatment	Baseline	Dipper	Nondipper	Total
4 Sprays (N=xx)	Dipper	xx (xx.x)	xx (xx.x)	xx(xx.x)
	Non-Dipper	xx(xx.x)	xx(xx.x)	xx(xx.x)
	Total	xx(xx.x)	xx(xx.x)	xx(xx.x)
8 Sprays (N=xx)	Dipper	xx(xx.x)	xx(xx.x)	xx(xx.x)
	Non Dipper	xx(xx.x)	xx(xx.x)	xx(xx.x)
	Total	xx(xx.x)	xx(xx.x)	xx(xx.x)
Placebo (N=x)	Dipper	xx(xx.x)	xx(xx.x)	xx(xx.x)
	Nonipper	xx(xx.x)	xx(xx.x)	xx(xx.x)
	Total	xx(xx.x)	xx(xx.x)	xx(xx.x)

Dipper: ≥10% decrease in nighttime ambulatory systolic blood pressure (SBP) versus the daytime ambulatory SBP.
Nondipper: <10% decrease in nighttime ambulatory SBP versus daytime ambulatory SBP.
Note: Percentages are based on the number of subjects in each treatment group. Subjects in the ABP who are missing any component necessary to calculate dipping are excluded from this table.
Source: Listing 16.2.6.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Table 14.3.1.1

Overall Summary of Treatment-Emergent Adverse Events (Safety Population)

		B244				
	Statistic	4 Sprays (N=xx)	8 Sprays (N=xx)	All B244 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Subjects with at Least 1 Treatment-Emergent Adverse Event (TEAE)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with at Least 1 Treatment-Related TEAE	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with at Least 1 Grade 3 or 4 TEAE	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with at Least 1 Treatment-Related Grade 3 or 4 TEAE	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with at Least 1 Serious TEAE	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with at Least 1 Treatment-Related Serious TEAE	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

If a subject experiences multiple occurrences in the category of Adverse event , the subject will be counted only once for that PT/SOC.
If a subject experiences the same AE more than once with different CTCAE grades, the event with the highest grade will be tabulated.
TEAE is defined as any AEs that begin or worsen on or after the start of study drug through 30 days after the last dose of study drug.
Treatment-related TEAE is defined as TEAE that was considered by the Investigator to be at least possibly related to the study drug.
Severity will be graded based on the NCI CTCAE, Version 4.03.
Adverse events are coded using MedDRA v19.0.
Source: Listing 16.2.7.1

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Table 14.3.1.2

Treatment-Emergent Adverse Events (TEAE) by MedDRA System Organ Class and Preferred Term (Safety Population)

		B244				
	Statistic	4 Sprays (N=xx)	8 Sprays (N=xx)	All B244 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Any TEAE	n (%)	xx (xx.x	xx (xx.x	xx (xx.x	xx (xx.x	xx (xx.x
System Organ Class 1						
Preferred Term 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.						
System Organ Class 2						
Preferred Term 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.						
Etc.						

TEAE is defined as any AEs that begin or worsen on or after the start of study drug through 30 days after the last dose of study drug.
If a subject experiences multiple occurrences in the same PT/SOC, the subject will be counted only once for that PT/SOC.
Adverse events are coded using MedDRA v19.0.
Source: Listing 16.2.7.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat Table 14.3.1.2 for the following tables:

Table 14.3.1.3 Treatment-Related Treatment-Emergent Adverse Events (TEAE) by MedDRA System Organ Class and Preferred Term (Safety Population)
PROGRAMMING NOTE: filter for at least possibly related to the study drug. Add footnote "Treatment-related TEAE is defined as TEAE that was considered by the Investigator to be at least possibly related to the study drug."

Table 14.3.1.4 Grade 3 or 4 Treatment-Emergent Adverse Events (TEAE) by MedDRA System Organ Class and Preferred Term (Safety Population)
PROGRAMMING NOTE: filter for grade = 3 or 4. Add footnote "Severity will be graded based on the NCI CTCAE, Version 4.03." AND "If a subject experiences the same AE more than once with different CTCAE grades, the event with the highest grade will be tabulated."

Table 14.3.1.5 Treatment-Related Grade 3 or 4 Treatment-Emergent Adverse Events (TEAE) by MedDRA System Organ Class and Preferred Term (Safety Population)
PROGRAMMING NOTE: filter for grade = 3 or 4 and at least possibly related to the study drug. Add footnote "Treatment-related TEAE is defined as TEAE that was considered by the Investigator to be at least possibly related to the study drug." AND "Severity will be graded based on the NCI CTCAE, Version 4.03." AND "If a subject experiences the same AE more than once with different CTCAE grades, the event with the highest grade will be tabulated."

Table 14.3.1.6 Serious Treatment-Emergent Adverse Events (TEAE) by MedDRA System Organ Class and Preferred Term (Safety Population)
PROGRAMMING NOTE: filter for SERIOUS = YES.

Repeat Listing 16.2.7.1 for the below table listings.

Table 14.3.2.1 Serious Adverse Events
PROGRAMMING NOTE: filter for SERIOUS = YES and remove Serious? Column.

Table 14.3.2.2 Adverse Events Leading to Early Discontinuation
PROGRAMMING NOTE: filter for subjects who discontinued early.

Table 14.3.2.3 Subject Deaths
PROGRAMMING NOTE: filter for subject deaths, remove Outcome column and accompanying footnote and renumber other footnotes accordingly.

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Table 14.3.5.1

Summary of Values and Change from Baseline for Chemistry Parameters (Safety Population)

Parameter: xx

		B244							
		4 Sprays (N=xx)		8 Sprays (N=xx)		All B244 (N=xx)		Placebo (N=xx)	
Visit	Statistic	Value	Change from Baseline	Value	Change from Baseline	Value	Change from Baseline	Value	Change from Baseline
Baseline	n	xx	-	xx	-	xx	-	xx	-
	Mean	xx.x		xx.x		xx.x		xx.x	
	(SD)	(xx.xx)		(xx.xx)		(xx.xx)		(xx.xx)	
	Median	xx.x		xx.x		xx.x		xx.x	
	Min, Max	xx, xx		xx, xx		xx, xx		xx, xx	
Day 28	n	xx	xx	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	(SD)	(xx.xx)	(xx.xx)	(xx.xx)	(xx.xx)	(xx.xx)	(xx.xx)	(xx.xx)	(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

Source: Listing 16.2.8.1.1, Listing 16.2.8.1.2

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Continue for all chemistriy parameters.

Repeat for:
Table 14.3.5.2 Summary of Values and Change from Baseline for Vital Parameters (Safety Population)

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Table 14.3.5.3

Electrocardiogram – Shift in Interpretation from Baseline to Day 28 (Safety Population)

			Day 28 Visit				
Treatment	Interpretation	Baseline n	Normal n (%)	Abnormal, NCS n (%)	Abnormal, CS n (%)	Missing n (%)	Total n (%)
B244	Normal	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal, NCS	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal, CS	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Missing	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Total	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Placebo	<as above>						

Source: Listing 16.2.9.2

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

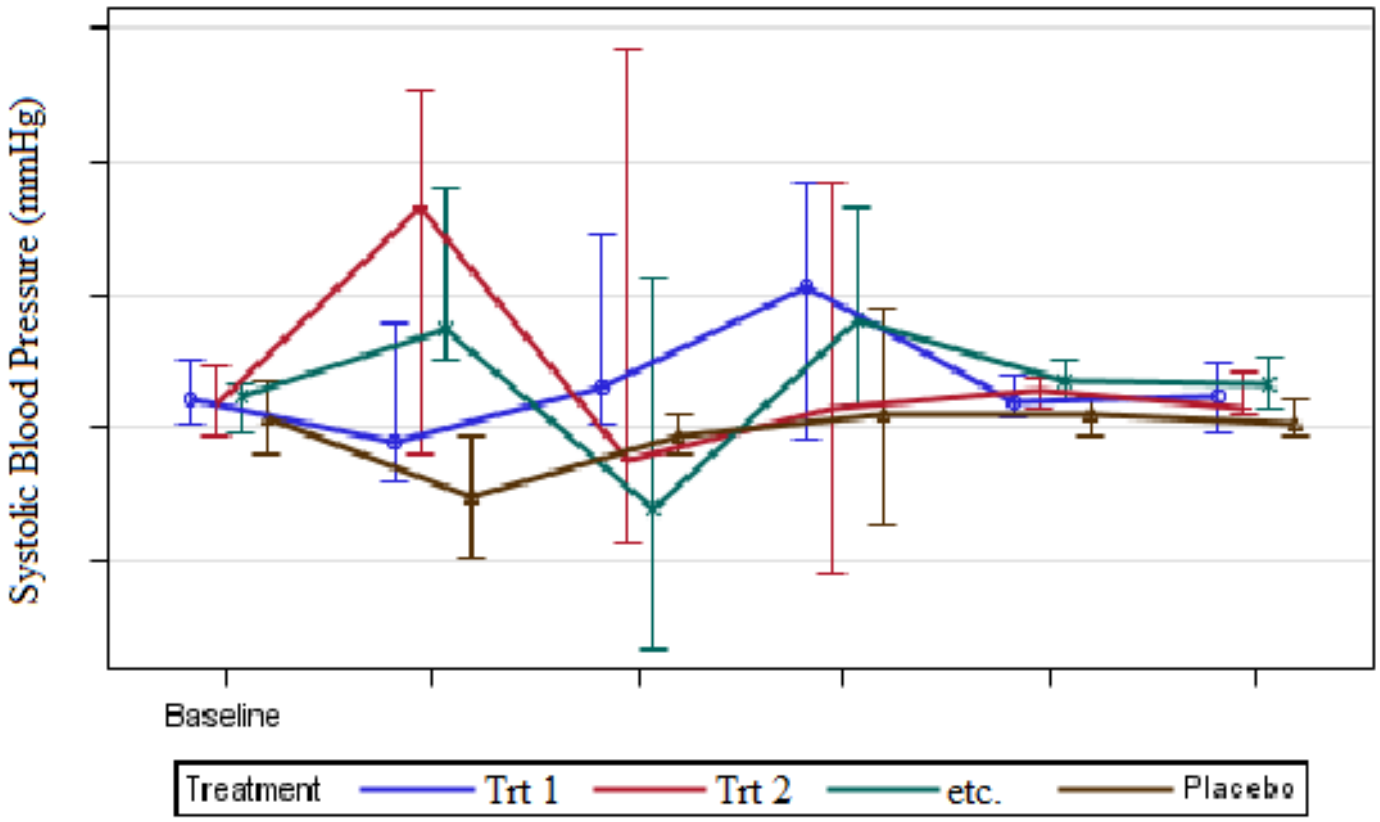
7.1.2. Statistical Figure Shells

The following figures will be produced.

STATISTICAL FIGURES

Figure 14.2.1.1A

Line Plot of Systolic and Diastolic Blood Pressure over Time by Treatment (ITT Population)



Source: Table 14.2.1A

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for:
Figure 14.2.1.1B Line plot of Systolic and Diastolic Blood Pressure over Time by Treatment (PP Population)

Figure 14.2.2

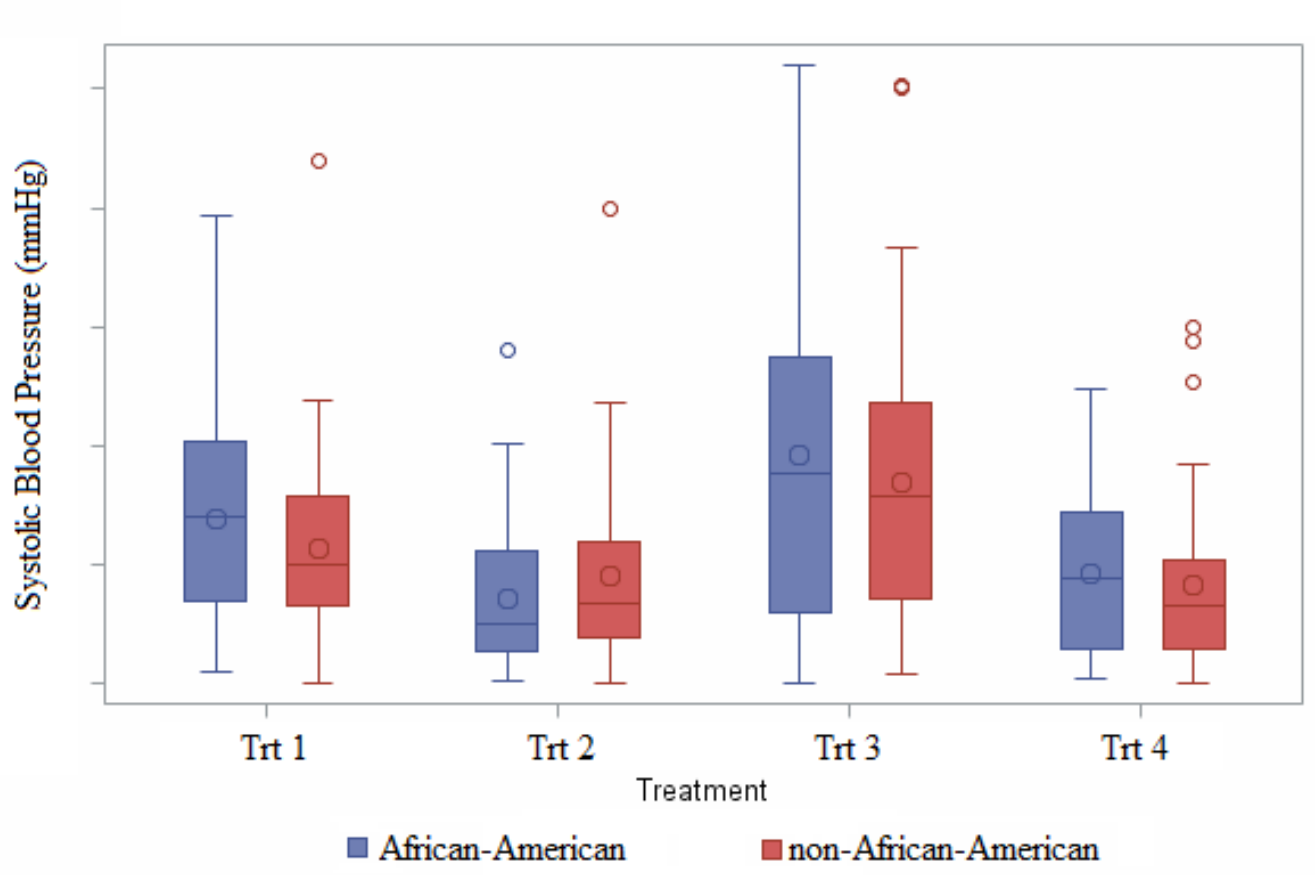
Change from Baseline in Systolic and Diastolic Blood Pressure over Time

Figure 14.2.3

Ambulatory Blood Pressure by Treatment – Averaged Time Point Values (Box Plot)

Figure 14.2.4A

Box Plot of Systolic Blood Pressure over Time by Treatment by Race (ITT Population)



Source: Table 14.2.1C

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for:
Figure 14.2.4B Box Plot of Systolic Blood Pressure over Time by Treatment by Hypertension Stage (ITT Population)
Figure 14.2.4C Box Plot of Systolic Blood Pressure over Time by Treatment by Gender (ITT Population)
Figure 14.2.4D Box Plot of Systolic Blood Pressure over Time by Treatment by Age Group (ITT Population)

Figure 14.2.5

Box Plot of Change from Baseline in In-Clinic by Treatment and Subgroup

Figure 14.2.6

Box Plot of Change from Baseline in Ambulatory Blood Pressure Average Time Point Values by Treatment and Subgroup

7.1.3. Data Listing Shells

The following listings will be produced.

SUBJECT DATA LISTINGS

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Listing 16.2.1

Study Completion Status (Enrolled Subjects)

Teatment:
Strata:

	Subject in Population									
Subject Number	ITT	Safety	PP	ABPP	Date of Randomization	Date of Drug Dispense	Date of Last Dose (Rel Day)	Date of Study Withdrawal (Rel Day)	Reason for Early Study Discontinuation	Protocol Version
									Death Lost to Follow-up Withdrawal of Consent by Subject Investigator's Decision Screen Failure Other, specify	

Intent-to-Treat (ITT) Population: All randomized subjects, analyzed according to treatment assigned.
Safety Population: All subjects who received at least 1 dose of study medication, analyzed according to drug received.
Per Protocol (PP) Population: Subjects who were administered at least 50% of study medication, have baseline and at least 1 post-baseline in-clinic systolic or diastolic blood pressure measurement, and did not have any major protocol violations which could potentially compromise interpretation of results.
Ambulatory Blood Pressure Monitoring Population (ABPP): Subjects in the Safety population who had valid baseline and Day 28 ABPM measurements. Subjects who repeated the ABPM are included in the population if the repeated assessment met the Monitor’s criteria for “passing.”
Rel Day = Relative to first dose of study medication, Day 1.

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Listing 16.2.2.1

Inclusion/Exclusion Criteria Not Met

Treatment:
Strata:

Subject Number	Did the Subject Meet All Eligibility Criteria?	Criterion ID Not Met	Was a Waiver Provided so the Subject can CContinue on the Trial?	Date of Waiver
		Inclusion 1	Yes	DD-MMM-YYYY
		Inclusion 2	No	
		Etc.		

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX | DATE: HH:MM/DDMMMYYYY

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Listing 16.2.2.2

Protocol Deviations

Treatment:
Strata:

Subject Number	Date	Visit	Description

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.3

Subjects Excluded from Efficacy Analyses

Treatment:
Strata:

Subject Number	Reason Excluded from PP Population

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.4.1

Demographics and Baseline Information

Treatment:
Strata:

Subject Number	Age (years)	Sex	Race	Ethnicity	Height (cm)	Weight (kg)	BMI (kg/m^2)	Is Female Subject of Child-Bearing Potential?	If Yes, Form of Birth Control	If No, Reason
			American Indian or Alaska Native Asian Black or African-American Native Hawaiian or Other Pacific Islander White Other	Hispanic or Latino Not Hispanic or Latino Not Reported Unknown				Yes No	Condom (w/spermicide) Oral Patch Cervical Cap (w/spermicide) Vaginal Ring Vasectomized Partner Abstinence Diaphragm (w/spermicide) IUD Other	Post-Menopausal Surgically Sterile Hysterectomy Tubal Ligation Other, Specify

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Listing 16.2.4.2

Smoking History

Treatment:
Strata:

Subject Number	Subject Have Smoking History	Type of Product Smoked	Date Subject Started to Smoke	Still Smoking?	Date Stopped Smoking	Number of Packs Per Day (Tobacco Products)	Number of Times Smoking Occurs per Week (non-tobacco products)
	Yes	Tobacco Products		Yes			
	No	Non-Tobacco Products		No			
		Both					

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

DATE: HH:MM/DDMMMYYYY

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Listing 16.2.4.3

Medical History

Treatment:
Strata:

Subject Number	Medical History Condition/Event Description	MedDRA System Organ Class	Preferred Term	Date Diagnosed	Ongoing at Screening?	End Date	Currently Being Treated with Concomitant Medication?
							Yes
							No

Medical history is coded using MedDRA v19.0.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.4.4

Additional Medical History

Treatment:
Strata:

Subject Number	Medical History Question	Response
	Suffer from Depression	Yes
	Mediaction for Depression	No
	Etc.	

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: List question and answer for any variable answered "yes" or with a numerical value.

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Listing 16.2.5.1

Dosing Data

Treatment:
Strata:

Subject Number	Visit	Date/Time of Dispense (Rel Day)	Weight of Investigational Product (mg)

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.5.2

Extent of Exposure

Treatment:
Strata:

Subject Number	Baseline Weight of Study Drug [1]	Week 4 Weight (g)	Amount of Product Used (g) [2]	Expected Weight	Percent Compliance [3]

[1] Cumulative study drug exposure = weight of the 3 drug bottles at last visit - weight of the 3 drug bottles at first dispense.
[2] Amount of product used per day = change / number of days the subject was on treatment.
[3] Percent compliance = (Net weight of study drug)/(Expected weight for 28 days of use)×100.

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Listing 16.2.6.1

Systolic and Diastolic Blood Pressure

Treatment:
Strata:

Subject Number	Visit	Date/Time (Rel Day)	Subject Sitting for >5 Minutes?	Systolic Blood Pressure (mmHg)				Diastolic Blood Pressure (mmHg)				Heart Rate (BPM)			
				Reading 1	Reading 2	Reading 3	Avg	Reading 1	Reading 2	Reading 3	Avg	Reading 1	Reading 2	Reading 3	Avg
			Yes												
			No												

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.6.2

Ambulatory Blood Pressure Monitoring - All Results

Treatment:
Strata:

Subject Number	Visit	ABPM Start Date	Reading Time	Clock Hour	Dose Hour	Diastolic Blood Pressure	Systolic Blood Pressure	Heart Rate	Mean Arterial Pressure (MAP)	Error Code	Comments

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Listing 16.2.6.3

Ambulatory Blood Pressure Monitoring - Hourly Averages

Treatment:
Strata:

Subject Number	Visit	ABPM Start Date	Clock Hour	Dose Hour	Diastolic Blood Pressure	Systolic Blood Pressure	Heart Rate	Mean Arterial Pressure (MAP)	Number of Readings

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.7.1

Adverse Events by Subject

Treatment:
Strata:

Subject Number	Start Date/ Time (Rel Day)	Stop Date/ Time (Rel Day)	SOC/PT	Description	Severity / Grade	Serious?	Serious Criteria	Outcome [2]	Relation-ship [3]	Action Taken [4]	Discontinued from Study
					Mild / Grade 1 Mod. / Severe	Yes No					

Adverse events are coded using MedDRA v19.0.
Rel Day = Relative to first dose of study medication, Day 1.
[1] Severity will be graded based on the NCI CTCAE, Version 4.03.
[2] R = Resolved , NR = Not Resolved.
[3] Treatment-related TEAE is defined as TEAE that was considered by the Investigator to be at least possibly related to the study drug. Relationship decode: Rel = Related, Poss = Possibly Related, Prob = Probably Related, Unl = Unlikely Related, Unr = Definitely Not Related.
[4] Action taken decode: None, Med = Concomitant Medication, Stop = Drug Stopped, Oth = Other.

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Listing 16.2.8.1.1

Hematology – Part 1

Treatment:
Strata:

Subject Number	Visit	Date/ Time of Collection	Rel Day	Subject Fasting?	WBC (10^3/uL)	RBC (10^6/uL)	Hematocrit (%)	Hemoglobin (g/dL)	Platelets (10^3/uL)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW (%)

CS = Clinically Significant, NCS = Abnormal, Not Clinically Significant.
Rel Day = Relative to first dose of study medication, Day 1.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Continue for all hematology parameters in:
Listing 16.2.8.1.2 Hematology – Part 2

Repeat for all chemistry parameters in:
Listing 16.2.8.2.1 Chemistry – Part 1
Listing 16.2.8.2.2 Chemistry – Part 2

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Listing 16.2.8.3

Urine Pregnancy Test

Treatment:
Strata:

Subject Number	Visit	Date Performed	Rel Day	Pregnancy Test Done?	Reason Not Done	Test Result
					Not Childbearing Potential Female	Positive
					Other	Negative

Rel Day = Relative to first dose of study medication, Day 1.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Report for females only.

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Listing 16.2.9.1

Vital Signs

Treatment:
Strata:

Subject Number	Visit	Date/ Time of Collection	Rel Day	Diastolic Blood Pressure (mmHg)	Heart Rate (BPM)	Weight (kg)

Rel Day = Relative to first dose of study medication, Day 1.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.9.2

12-Lead Electrocardiogram

Treatment:
Strata:

Subject Number	Visit	Date Performed	Rel Day	Resting Supine for >5 Minutes?	PR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	RR Interval (msec)	QTc Interval (QTcB; Bazett's correction) (sec)	Assessment
										Normal
										Abnormal, NCS
										Abnormal, CS

CS = Clinically Significant, NCS = Abnormal, Not Clinically Significant.

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Listing 16.2.9.3

Soap and Shampoo

Treatment:
Strata:

Subject Number	Visit	Date of Follow-up	Rel Day	Consistently [1] Using Provided Soap and Shampoo?	If No, Reason	Other Shampoo/ Soap Used	Frequency Since Last Visit	Plan to Use Sponsor-Provided Soap/ Shampoo Moving Forward?	Refraining from Makeup Use?	If No, Days per Week of Makeup Use	Return Remaining Soap/ Shampoo?	Compliant With IP Since Last Visit?	Number of Missed Applications
				Yes No			<5 Times 5-10 Times >10 Times			1-2 Days 2-4 Days 4+ Days			

[1] Consistently meaning they have not used any other soap or shampoo more than once or twice since the last visit.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.9.4

Concomitant Medications

Treatment:
Strata:

Subject Number	Anatomic Therapeutic Class	Preferred Term	Start Date (Rel Day)	Stop Date (Rel Day)	Ongoing?	Dose Per Adminis-tration	Dose Unit	Route	Frequency

Rel Day = Relative to first dose of study medication, Day 1.
Concomitant medications are any medications that did not end prior to first dose. If an end date is missing or the medication is ongoing, the medication is included.
Concomitant medications anatomic therapeutic class (ATC) and preferred term (PT) are coded using the WHO Drug Dictionary version March 2016.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.9.5

Physical Exam

Treatment:
Strata:

Subject Number	Visit	Date	Rel Day	Body System	Result

Rel Day = Relative to first dose of study medication, Day 1.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Concetatenate Result + Finding if result is abnormal. Do not present "Not Done" results.